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ORIGINAL RESEARCH

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The role of follow-up CA15-3 in prognosis of breast cancer

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Abstract

Background: The purpose of this study is to confirm the usefulness of Cancer Antigen 15-3 (CA15-3) follow-up. We determine whether the change in the values of breast cancer tumor marker CA15-3 before and after treatment is useful as a prognostic factor for disease progression. **Methods**: We conducted a retrospective cohort study of female patients who were newly diagnosed with primary breast cancer. CA15-3 levels were checked 1 month preoperatively and at 1 year (Y) postoperatively. Disease-free survival and metastasis-free survival were analyzed according to CA15-3 levels and changes. **Results**: We analyzed the prognostic effect of the CA15-3 levels. Lymph node metastasis and postoperative 1Y CA15-3 levels were significant factors of disease-free survival. And elevated postoperative 1Y CA15-3 level was the only significant prognostic factor for metastasis-free survival. The study groups were classified into four subgroups according to the changes in CA15-3 level (preoperative–postoperative 1Y CA15-3). The normal-normal group showed the best disease-free and metastasis-free survival, while the elevated-elevated group showed the worst survival. **Conclusions**: We found that persistently high CA15-3 levels after the initial treatment might be a significant prognostic factors of worse breast cancer prognosis.

Keywords

Breast cancer; Tumor marker; CA15-3

1. Introduction

According to 2021 National cancer information center, among all Korean women, breast cancer is the most common prevalent cancer and the fourth most common cause of cancer-related death. Despite effective early detection and the improvements in treatments, a substantial number of patients with breast cancer develop recurrence after initial treatment.

Most previous studies have evaluated the prognostic values of tumor and patient characteristics and results of tests, including blood test at diagnosis especially before treatment, however studies that evaluate test results obtained after treatment as prognostic markers remain limited. Imaging examinations such as computed tomography imaging and magnetic resonance imaging with contrast are used to identify disease recurrence, but these expensive techniques are invasive to patients and characterized by hazard of radiation. Moreover, none are ideal for early prediction of disease progression. Tumor evaluation such as complete remission after neoadjuvant chemotherapy or Ki-67 level after preoperative endocrine therapy can also be useful surrogate markers of prognosis [1–3].

Cancer antigen 15-3 (CA15-3) is still widely used as a serum biomarker in the management of patients with breast cancer at the time of disease diagnosis, post treatment surveillance follow-up, and monitoring response to therapy in metastatic patients [4]. However, some studies have shown that CA15-3 had limitations as early detection of disease with low sensitivity and specificity. And its role in monitoring patients without overt disease has not been established [5, 6].

The purpose of this study is to determine whether the change in the values of breast cancer tumor marker CA15-3 before and after treatment is useful as a prognostic factor for disease progression.

2. Methods

We conducted a retrospective study of female patients who were newly diagnosed with primary breast cancer from June 2015 to June 2020 at a single institute. The exclusion criteria were as follows: patients who were concurrently diagnosed with cancers in other organs; patients who had distant metastasis on diagnosis; patients who had preoperative systemic therapy; and patients who developed recurrence and/or distant metastasis within one year after operation. Patients who did not have preoperative CA15-3 and follow-up CA15-3 values were also excluded.

To identify the prognostic impact of CA15-3 levels, clini-

cal features, histopathological findings, and follow-up results were reviewed. CA15-3 levels were measured using an immunoradiometric assay, and less than 25 U/mL was considered normal. Patients were recommended adjuvant therapy and surveillance according to the St. Gallen or National Comprehensive Cancer Network (NCCN) guidelines [7, 8]. CA15-3 values were also included in our surveillance protocol. Preoperative CA15-3 levels were checked within 1 months preoperatively and postoperative 1Y CA15-3 levels were determined as the levels that were checked between 9–15 months after operation (mean ± standard deviation (SD); 12.90 ± 1.09 months).

A disease-specific event was defined as a locoregional recurrence or distant metastasis during follow-up. Disease-free survival (DFS) was defined as the time from the date of operation to the first diagnosis of a disease-specific event or last follow-up. Metastasis-free survival (MFS) was defined as the time from the date of operation to the first diagnosis of a distant-metastasis or the last follow-up.

Continuous variables were analyzed using the student's *t*-test or a one-way analysis of variance, and categorical variables were analyzed using the chi-squared test. Survival was analyzed using the Kaplan-Meier method and compared using the log-rank test. A Cox proportional hazards model was used to identify the factors significantly associated with DFS and MFS. All statistical analyses were performed using SPSS version 20.0 (SPSS, Inc, Chicago, IL, USA), and statistical significance was defined as $p < 0.05$.

3. Results

In total, 202 female patients with breast cancer were included in this study, and the median age at diagnosis was 53 (range 29–87) years. The mean preoperative CA15-3 level was 11.59 (range 3.38–72.63) U/mL and elevated levels were identified in 11 (5.4%) of the participants, respectively. The mean postoperative 1Y CA15-3 were 11.13 (range 0.74–174.20) U/mL and elevated levels were also identified in 11 (5.4%) of the participants, respectively. Patient follow-up periods ranged from 20 to 109 months (mean, 55.567 ± 11.23 months), during which there were 24 disease specific events and 17 distant metastatic events (Table 1).

The mean preoperative CA15-3 level was significantly elevated in patients with a disease-specific event (11.19 ± 7.46 *vs.* 14.41 ± 10.40, $p = 0.008$) and in patients with a distant-metastatic event (11.16 ± 7.50 *vs.* 16.32 ± 10.74, $p = 0.013$). The mean postoperative 1Y CA15-3 was also elevated in patients with disease-specific event (9.77 ± 6.86 *vs.* 20.76 ± 34.87, $p < 0.001$) and in patients with a distant-metastatic event (9.93 ± 7.36 *vs.* 24.28 ± 29.72, $p < 0.001$).

We analyzed the prognostic effect of the CA15-3 levels. Lymph node metastasis, high histologic grade and elevated preoperative CA15-3 and postoperative 1Y CA15-3 levels were significant prognostic factors for disease-free survival. However, lymph node metastasis and postoperative 1Y CA15-3 levels are only significant in the multivariate analysis. In particular, elevated postoperative 1Y CA15-3 levels were the most powerful prognostic factor for a poor disease-free survival (hazard ratio (HR) = 4.291, $p = 0.006$) (Tables 2 and 3).

TABLE 1. Characteristics of the study population.

	Number	%
Age		
Mean ± SD, yr	54.89 ± 10.90	
≤50	79	39.1
>50	123	60.9
T stage		
T1	117	57.9
T2–4	85	42.1
N stage		
N0	144	71.3
N1–3	58	28.7
Estrogen receptor		
Positive	156	77.2
Negative	46	22.8
Progesterone receptor		
Positive	136	67.3
Negative	66	32.7
Her-2		
Positive	68	33.7
Negative	130	64.4
Unknown	4	2.0
Histologic grade		
Grade 1	49	24.3
Grade 2–3	149	73.8
Unknown	4	2.0
Preoperative CA15-3		
Mean ± SD	11.59 ± 7.92	
Normal	191	94.6
Elevated	11	5.4
Postoperative 1Y CA15-3		
Mean ± SD	11.13 ± 14.12	
Normal	191	94.6
Elevated	11	5.4
Disease-specific event	24	11.9
Distant metastatic event	17	8.4

SD: standard deviation; Her-2: human epidermal growth factor receptor 2; CA: Cancer Antigen; 1Y: 1 year.

We also analyzed the prognostic factors for metastasis-free survival. High histologic grade and elevated preoperative CA15-3 and postoperative 1Y CA15-3 levels were identified as significant prognostic factors for metastasis-free survival. In multivariate analysis, an elevated postoperative 1Y CA15-3 level was the only significant prognostic factor for metastasis-free survival (HR = 5.675, $p = 0.004$) (Tables 2 and 3).

The study groups were classified four subgroups according to the changes in CA15-3 level (preoperative–postoperative 1Y CA15-3). CA15-3 values below 25 were marked as nor-

TABLE 2. Univariate analysis of disease-free survival and metastasis-free survival.

	Disease-free survival		Metastasis-free survival	
	Median survival (mon)	Univariate analysis (Log-Rank, *p* value)	Median survival (mon)	Univariate analysis (Log-Rank, *p* value)
Age (yr)				
≤50	56.50	0.844	56.83	0.774
>50	58.31		58.50	
T stage				
T1	59.14	0.203	59.14	0.998
T2–4	55.00		55.56	
N stage				
N0	58.65	0.020	58.78	0.082
N1–3	54.50		55.60	
Estrogen receptor				
Positive	58.24	0.073	58.27	0.179
Negative	56.33		56.80	
Progesterone receptor				
Positive	57.67	0.358	57.78	0.404
Negative	58.17		58.83	
Her-2				
Positive	59.26	0.474	59.21	0.785
Negative	55.36		55.80	
Histological grade				
Grade 1	59.15	0.011	59.00	0.063
Grade 2–3	56.67		57.38	
Preoperative CA15-3				
Normal	58.05	0.001	58.26	0.004
Elevated	45.00		45.00	
Postoperative 1Y CA15-3				
Normal	57.91	<0.001	58.09	<0.001
Elevated	47.00		52.60	

Her-2: human epidermal growth factor receptor 2; CA: Cancer Antigen; 1Y: 1 year.

TABLE 3. Multivariate analysis of disease-free survival and metastasis-free survival.

	Disease-free survival		Metastasis-free survival	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
N stage				
N0	2.494 (1.106–5.625)	0.028	1.837 (0.702–4.812)	0.215
N1–3				
Estrogen receptor				
Positive	2.229 (0.932–5.333)	0.072		
Negative				
Histological grade				
Grade 1	7.076 (0.941–55.192)	0.057	5.055 (0.664–38.482)	0.118
Grade 2–3				
Preoperative CA15-3				
Normal	2.427 (0.688–8.562)	0.168	1.885 (0.457–7.766)	0.380
Elevated				
Postoperative 1Y CA15-3				
Normal	4.291 (1.506–12.225)	0.006	5.675 (1.739–18.521)	0.004
Elevated				

CI: confidential interval; HR: hazard ratio; CA: Cancer Antigen; 1Y: 1 year.

mal and 25 or more were marked as elevated. The normal-normal group showed the best disease-free and metastasis-free survival, while the elevated-elevated group showed the worst survival (Log-rank $p < 0.001$) (Fig. 1, Table 4).

4. Discussion

CA15-3 is a member of the mucin glycoproteins family (MUC1) that is heterogeneously expressed on the apical surface of normal epithelial cells, including those of the breast [9, 10]. Although current guidelines such as the NCCN guidelines, do not recommend its use for routine surveillance [8], CA15-3 is still widely used as a tumor marker in the management of patients with breast cancer at the time of diagnosis, during postoperative surveillance, and in evaluation of the therapeutic response.

Elevated serum CA15-3 levels were more frequently observed in patients in the luminal subgroup, particularly in those with metastatic breast cancer [11, 12]. However, conflicting results have been reported in the preoperative settings for breast cancer. Li H. *et al*. [13] showed significantly higher CA15-3 levels in the luminal type than human epidermal growth factor receptor 2 (Her-2) and triple negative type breast cancer, but Shao *et al*. [14] showed significantly higher rates with higher elevated CA15-3 in Her-2 and triple negative groups. The remaining studies did not find any significant differences between subgroups [15–17].

Numerous studies have also determined the correlation between tumor markers and breast cancer prognosis. In a study of 10,836 Chinese female patients with breast cancer, preoperative CA15-3 levels differed according to molecular subtype and had significant prognostic power for survival (breast cancer-specific survival, HR (95% confidence interval (CI)) 1.54 (1.01–2.34), $p = 0.04$; disease-free survival, HR (95% CI) 2.09 (1.44–3.02), $p < 0.01$) [18]. Another recent study showed that preoperative CA15-3 levels were significantly higher in the occult metastasis group (defined as patients that had no metastasis at the time of diagnosis but developed metastasis within 3 years after treatment) than in the control group [18]. Some studies have investigated changes in CA15-3 levels during follow-up. In a study of patients in the International Breast Cancer Study Group (IBCSG) trials VIII [19] and IX [20], one or more abnormal CA15-3 levels during follow-up were associated with breast cancer recurrence (relapse-free survival, HR (95% CI) 1.97 (1.70–2.28), $p < 0.0001$) [21].

This study, we attempted to confirm the prognostic value of a preoperative CA15-3 level and approximately one-year postoperative CA15-3 levels. In particular, the postoperative

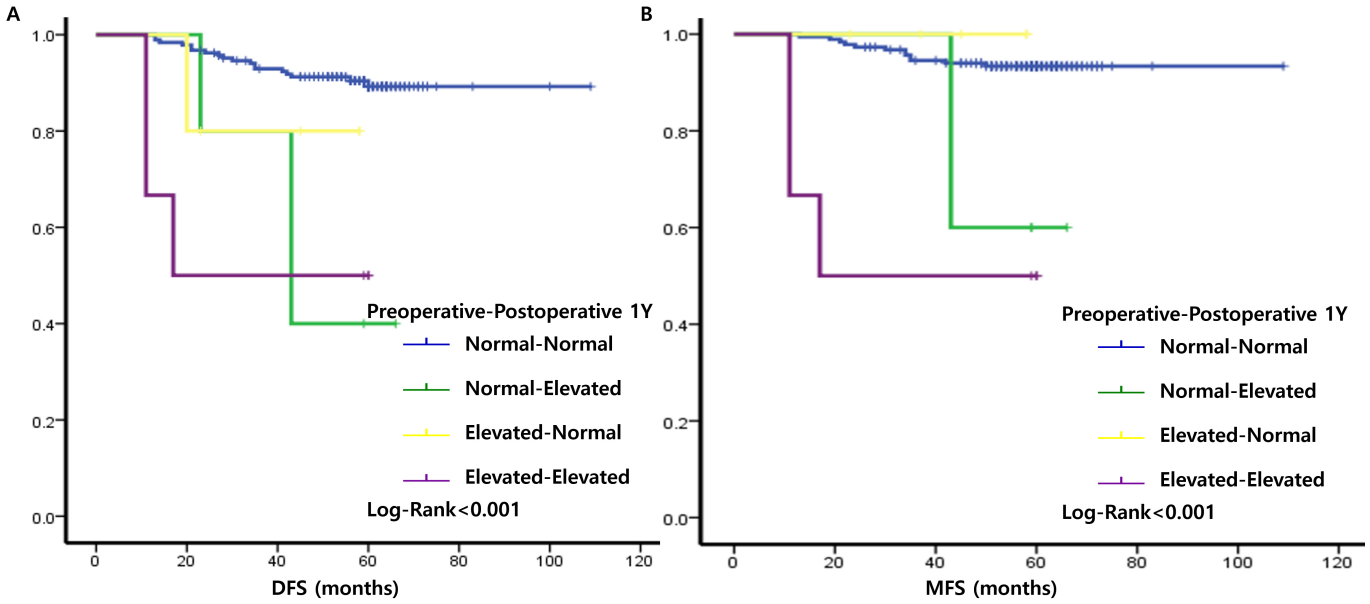

FIGURE 1. Kaplan-Meier curve according to subgroups of CA15-3 level change. (A) Disease-free survival. (B) Metastasis-free survival. 1Y: 1 year; DFS: Disease-free survival; MFS: Metastasis-free survival.

TABLE 4. Analysis of prognostic effect of CA15-3 level changes.

Preoperative–postoperative 1Y CA15-3 (Number)	Disease-specific event			Metastasis-specific event		
	Number (%)	Mean DFS	Log-Rank, *p* value	Number (%)	Mean MFS	Log-Rank, *p* value
Normal-Normal (186)	18 (9.7%)	55.26	<0.001	12 (6.5%)	55.89	<0.001
Normal-Elevated (5)	3 (60.0%)	46.80		2 (40.0%)	54.00	
Elevated-Normal (5)	1 (20.0%)	40.80		0 (0.0%)	44.20	
Elevated-Elevated (6)	3 (50.0%)	36.33		3 (50.0%)	36.33	

DFS: disease-free survival; MFS: metastasis free survival; CA: Cancer Antigen; 1Y: 1 year.

1Y CA15-3 level was analyzed to confirm whether changes in this level were more effective in predicting prognosis. As in the results of previous studies, it was confirmed that an elevated preoperative CA15-3 level indicates a poor prognosis. The cutoff value of CA15-3 varies from 13–30 U/mL, *etc.* [4, 11–15, 17, 22, 23], but usually, it is usually based on a normal upper limit of 25 U/mL. In our study, when multivariable analysis was performed, postoperative 1Y CA15-3 was confirmed as a predictor of significant disease recurrence and distant metastasis.

Our study has several important limitations. Only a small number of patients were enrolled at our hospital. Therefore, we could not perform an analysis of breast cancer subgroups. Additionally, a longer follow up period may have increased the significance of the postoperative CA15-3 level.

We found that patients with persistently high CA15-3 levels after completion of the initial intensive treatment had a significantly worse breast cancer prognosis. Therefore, these results suggest that CA15-3 serial follow-up may be useful in predicting post-treatment prognosis.

5. Conclusions

In this study, we presented the significance of change in the values of breast cancer tumor marker throughout the diagnosis and treatment as a prognostic factor for disease progression. Persistently high CA15-3 levels after completion of the initial intensive treatment had a significantly worse breast cancer prognosis. Therefore, CA15-3 serial follow-up may be useful in predicting breast cancer prognosis.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

JYK and EJJ—conceived of and organized the study and was primarily responsible for drafting the manuscript. JYK and JMK—carried out collection of primary data and provided clinical input. SJK, JHP, HGK, TP and SHJ—confirmed patients' outcomes of recurrence and follow up results and guided statistical analysis. CYJ, YTJ and YJL—participated in the study design and helped to draft the manuscript. As corresponding author, EJJ—designed and coordinated the research and provided close guidance throughout the process. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study received approval and ethical clearance from the institutional review board of the Gyeongsang National University Hospital and met the guidelines of the responsible governmental agencies (IRB No. GNUH 2024-09-009). Informed consent was not required as deemed by the ethics committee due to the retrospective review of medical records.

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CONFLICT OF INTEREST

All authors declare that there is no actual or potential conflict of interest.

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