JBUON 2013; 18(3): 608-613
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Variations in tumor marker levels in metastatic breast cancer patients according to tumor subtypes

T. Kos[1], S. Aksoy[2], M.A.N. Sendur[1], Z. Arik[2], B. Civelek[1], N. Kandemir[1], N.Y. Ozdemir[1], N. Zengin[1], K. Altundag[2]

[1]*Ankara Numune Education and Research Hospital, Department of Medical Oncology, Ankara;* [2]*Hacettepe University Cancer Institute, Department of Medical Oncology, Ankara, Turkey*

Summary

Purpose: *To investigate whether serum CA 15-3 and CEA levels show differences among subgroups of breast cancer patients at the time of diagnosis of early-stage disease and at disease relapse.*

Methods: *Patients with metastatic breast cancer diagnosed from 2000 to 2010 were retrospectively analyzed. Data were obtained from medical charts. CA 15-3 and CEA levels of patients with metastatic disease at the time of diagnosis or who relapsed during follow-up were evaluated. Four different breast cancer subtypes were defined: estrogen receptor (ER) and/or progesterone receptor (PR) positive and HER-2 negative (luminal A), ER and/or PR positive and HER-2 positive (luminal B), ER and PR negative and HER-2 positive (HER-2 overexpressing) and triple negative (ER, PR and HER-2 negative). Fifty-eight (13.7%) of the patients were metastatic at the time of diagnosis.*

Results: *423 metastatic breast cancer patients were included. Of the patients, 232 (54.8%) had luminal A disease, 70 (16.5%) luminal B, 53 (12.5%) HER-2 overexpressing, and 68 (16.1%) triple negative disease. Preoperative CA 15-3 levels were raised in 48.1% of the luminal A group, in 42.8% of the luminal B group, in 26.0% of the HER-2 overexpressing group, and in 33.3% of the triple negative group. CA 15-3 levels after relapse were raised in 44.5% of the luminal A group, in 33.3% of the luminal B, in 28.9% of the HER-2 overexpressing, and in 38.8% of the triple negative group. Preoperative CEA levels were elevated in 44.3% of the luminal A group, in 28.5% of the luminal B, in 43.4% of the HER-2 overexpressing, and in 14.3% of the triple negative group. CEA levels after relapse were raised in 60.8%, 54.7%, 51.1%, and 36.0% of the patients in the 4 subgroups, respectively.*

Conclusion: *This study showed that there are differences between the breast cancer subgroups in terms of tumor marker levels in metastatic breast cancer patients. Tumor marker elevation was lower in the triple negative group as compared to the luminal groups. Monitoring CEA levels in luminal A group may be beneficial in determining early relapses. However, this retrospective study requires further prospective confirmative cohort studies.*

Key words: *breast cancer, cancer antigen 15-3, carcinoembryonic antigen, subgroups*

Introduction

Breast cancer is quite heterogeneous in terms of clinical disease progression. It has been possible via DNA microarray technology to understand better the heterogeneous structure of breast cancer by identifying subgroups. It has also been shown that these subgroups are crucial in evaluating the prognosis, medical therapy and response to treatment [1-4]. Immunohistochemical markers, which are biologically different and behave differently, are used to classify subgroups of breast cancer [5]. According to these markers, breast cancer can be divided into 4 major subgroups: luminal A and luminal B are characterized by high expression of ER and PR; HER-2 overexpressing is characterized by ER and PR negativity and HER-2 positivity, whereas triple-negative is characterized by negative expression of ER, PR and HER-2 [6].

Correspondence to: Kadri Altundag, MD. Hacettepe University Cancer Institute, Department of Medical Oncology, 06100, Sihhiye, Ankara, Turkey. Tel: +90 312 3052929, Fax: +90 312 3242009, E-mail: altundag66@yahoo.com
Received: 24/09/2012; Accepted: 18/10/2012

Although the exact benefits of breast cancer tumor markers, such as cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA), in relapses and in monitoring response to therapy have not been identified, they are being used as auxiliary tools. CA 15-3 is a glycoprotein expressed in various adenocarcinomas, especially in breast cancer [8]. FDA recommends CA15-3 to be used only in determining breast cancer relapses before the appearance of symptoms and in monitoring response to therapy. Although CA 15-3 has been found to have a lead time of 9 months before detection of relapse, it is not recommended as a screening test. Increased CA 15-3 levels show variations according to the stage of disease. In stages I and II, an increase of 20% has been reported, whereas an increase of nearly 70–80% is seen in later stages [7,8].

It has been shown that CA 15-3 levels reporesent not only a strong prognostic factor for advanced-stage breast cancer, but also an independent determinant for initial relapses [9]. There are some studies showing that patients with high levels of CA 15-3 have poor prognosis [10-13].

CEA is a high molecular weight glycoprotein and is elevated in more than 30% in metastatic and recurrent adenocarcinomas and especially in more than 50% in breast cancer metastases. Likewise, there are studies suggesting that changes in CEA levels might be associated with disease progression or regression. Some studies have suggested that tumor markers, such as CEA and CA 15-3 could be used in monitoring early relapses and response to therapy [14-18].

In the present study, we aimed to investigate whether serum CA 15-3 and CEA levels show differences among subgroups of breast cancer patients at the time of diagnosis of early-stage disease and at disease relapse (locoregional, metastatic).

Methods

Patient and tumor characteristics

Patients who had metastases at the time of diagnosis or developed metastasis during follow up, and who were followed up in Ankara Numune Education and Research Hospital, Department of Medical Oncology and Hacettepe University Institute of Oncology between 2000 and 2010 were retrospectively analyzed. Patient general and tumor characteristics and receptor status were obtained from medical charts. CA 15-3 and CEA levels of breast cancer patients, who were metastatic at the time of diagnosis or who developed relapse during follow-up period were retrospectively evaluated.

Immunohistochemical evaluation

ER, PR and HER-2 status of all cases were recorded from the pathology reports. Those who had < 1% nuclear staining of ER and PR using the immunoperoxidase method were accepted as negative. HER-2 status was graded from 0 to +3 by using immunohistochemistry (Hercept test) and fluorescent in situ hybridization (FISH).

Measurement of serum CA 15-3 and CEA

CA 15-3 and CEA levels were obtained from the patient files. Tumor markers were estimated with immune autoanalyzer by Chemiluminescent Microparticle Immunoassay (CMIA) original kits. CA 15-3 > 31U/mL, CEA > 3ng/mL for nonsmokers and > 7ng/mL for smokers were considered as high levels.

Statistics

Statistical analyses were performed by SPSS for Windows, version 13.0.(SPSS, Chicago, IL). The presence of normal distribution of the variables was tested using the Kolmogorov–Smirnov test. Inter-group percentages were compared by using chi-square test, whereas continuous variables were compared using the Student's t-test and Mann-Whitney U test, Wilcoxon W test and Kruskal-Wallis H test. Two-sided p values of <0.05 were considered statistically significant.

Results

A total of 423 patients were enrolled in this study. Their median age was 52 years (range 21–82). At the time of diagnosis 234 (55.3%) patients were premenopausal and 189 (44.7%) postmenopausal. Baseline patient and tumor characteristics are described in Table 1. Fifty-eight (13.7%) of the patients were metastatic at the time of diagnosis and the remaining developed metastasis during follow up. The most common sites for metastasis were bone (N=77, 18.2%), lung (N=50, 11.8%), liver (N=45, 10.6%) and locoregional (N=40, 9.5%). Invasive ductal carcinoma seen in 337 (79.7%) patients was the most common histological type. Other most commonly seen histological types were invasive lobular carcinoma (N=19, 4.5%), mixed type (N=34, 8.0%) and mucinous carcinoma (N=11, 2.6%). The majority of the tumors were grade 2 (N=155, 36.6%) and grade 3 (N=166, 39.2%). When considering all of the patients, preoperative median CA 15-3 level was 27.7 U/mL (range 6.5-3204.0) and preoperative median CEA level was 2.4 ng/mL (range 0.2-206.7), whereas on relapse the median CA 15-3 level was 32.9 U/mL

Table 1. General patient and disease characteristics

Characteristics	*N (%)*
Median age, years (range)	52 (21-82)
Menopausal status	
Premenopausal	234 (55.3)
Postmenopausal	189 (44.7)
Stage at diagnosis	
1	15 (3.5)
2	107 (25.3)
3	174 (41.1)
4	58 (13.7)
Metastatic site	
Local	40 (9.5)
Liver	45 (10.6)
Lung	50 (11.8)
Brain	21 (5.0)
Bone	77 (18.2)
Multiple	55 (13.0)
Other*	19 (4.5)
Histopathology	
Invasive ductal	337 (79.7)
Invasive lobular	19 (4.5)
Mixed	34 (8.0)
Other**	32 (7.6)
Tumor grade	
1	25 (5.9)
2	155 (36.6)
3	166 (39.2)
ER	
Positive	271 (64.1)
Negative	152 (35.9)
PR	
Positive	265 (62.6)
Negative	128 (30.3)
HER-2	
Positive	127 (30.0)
Negative	294 (69.5)
Subgroup	
Luminal A	232 (54.8)
Luminal B	70 (16.5)
HER-2 overexpressing	53 (12.5)
Triple negative	68 (16.1)
Tumor markers, median (range)	
Preoperative CA 15-3 U/mL	27.7 (6.5-3204.0)
Preoperative CEA ng/mL	2.4 (0.2-206.7)
Relapse CA 15-3 U/mL	32.9 (8.16-2455.0)
Relapse CEA ng/mL	3.6 (0.6-304.8)

* breast, intraabdominal, suprarenal, skin
**mucinous, metaplastic, medullary, neuroendocrine, invasive apocrine, invasive papillary, adenosquamous

(range 8.16-2455.0) and median CEA level was 3.6 ng/mL (range 0.6-304.8).

There was significant correlation between preoperative CA 15-3 and preoperative CEA levels (r=.44; p<0.001) levels and T stage (r=.17; p<0.001). There was statistically significant correlation between preoperative CEA levels and preoperative N stage (r=.16; p=0.05) and TNM stage (r=.24; p<0.009). No correlation was found with age, grade, and histology (Table 2).

Of the patients, 232 (54.8%) had luminal A, 70 (16.5%) luminal B, 53 (12.5%) HER-2 overexpressing, and 68 (16.1%) triple-negative disease. Distribution of patient characteristics among subgroups is shown in Table 3. The median age of the patients was similar in all subgroups. The number of premenopausal patients was higher in all subgroups and there was no statistically significant difference between the groups in terms of menopausal status (p=0.43). The patients in luminal B and in HER-2 overexpressing groups had more advanced stage, but the difference was not significant (p=0.40). The most common site of metastasis was the skeleton in the luminal groups (luminal A 23.3%; luminal B 20.0%). The most common site of metastasis was the liver in the HER-2 overexpressing group (20.8%) and locoregional in the triple-negative group (19.1%); the difference between the groups in terms of metastatic sites was statistically significant (p=0.03). Invasive ductal carcinoma was the most common histological type in all subgroups. The rate of mixed type was higher in luminal A, and the difference was significant (p=0.01). Tumor grade was better in the luminal groups as compared to the non-luminal groups (p=0.01).

Preoperative CA 15-3 levels were increased in 48.1% of the patients in luminal A, in 42.8% of the patients in luminal B, in 26.0% of the patients in HER-2 overexpressing and in 33.3% of the patients in triple-negative groups.

The rates of patients with increased CA 15-3 levels on relapse were as follows: 44.5% in luminal A, 33.3% in luminal B, 28.9% in HER-2 overexpressing and 38.8% in triple-negative cases. When the subgroups were compared, the rate of the patients with increased preoperative CA 15-3 levels was higher in luminal A group as compared to the non-luminal groups (p=0.09). The rate of patients with increased CA 15-3 levels upon relapse was higher again in luminal A group as compared to the non-luminal groups; however, the difference was not significant (p=0.09). The number of pa-

Table 2. Correlation risk factors with preoperative CEA levels

Preoperative CEA (ng/mL)	*Age*	*Grade*	*Tumor histology*	*T stage*	*N stage*	*TNM stage*	*Preoperative CA 15-3 (U/mL)*
r (correlation)	0.006	0.025	-0.005	0.17	0.16	0.24	0.44
p-value	0.94	0.76	0.94	<0.001	0.05	0.009	<0.001

Table 3. Distribution of the characteristics among subgroups

Characteristics	*Luminal A N=252*	*Luminal B N=70*	*HER-2 overexpressing N=53*	*Triple negative N=68*	*p-value*
Median age, years (range)	48 (24-89)	47.5 (21-78)	46 (21-84)	46 (27-81)	0.30
Menopausal status, N (%)					
Premenopausal	120 (51.7)	42 (60.0)	32 (60.4)	39 (57.4)	0.43
Postmenopausal	112 (48.3)	28 (40.0)	20 (37.7)	29 (42.6)	
Stage at diagnosis, N (%)					
1	10 (4.3)	2 (2.9)	0 (0)	3 (4.4)	
2	60 (25.8)	20 (28.6)	8 (15.1)	19 (27.9)	0.40
3	89 (38.4)	29 (41.5)	32(52.6)	28 (41.1)	
4	27 (11.6)	11 (15.7)	8 (15.1)	12 (17.6)	
Metastatic sites, N (%)					
Local	16 (6.9)	4 (5.7)	7 (13.2)	13 (19.1)	
Liver	19 (8.2)	12 (17.1)	11 (20.8)	3 (4.4)	
Lung	23 (9.9)	9 (12.9)	8 (15.1)	10 (14.7)	
Brain	6 (2.6)	3 (4.3)	4 (7.5)	8 (11.8)	0.03
Bone	54 (23.3)	14 (20.0)	4 (7.5)	5 (7.4)	
Multiple	36 (15.5)	8 (11.4)	6 (11.3)	5 (7.4)	
Other*	11 (4.7)	2 (2.9)	2 (3.8)	4 (5.8)	
Unknown	67 (26.6)	18 (25.7)	11 (20.8)	20 (29.4)	
Histopathology, N (%)					
Invasive ductal	179 (77.2)	64 (91.4)	43 (81.1)	51 (75.0)	
Invasive lobular	13 (5.6)	3 (4.3)	1 (1.9)	2 (2.9)	0.01
Mixed	24 (10.3)	3 (4.3)	5 (9.4)	2 (2.9)	
Other**	15 (6.4)	0 (0)	4 (7.6)	13 (19.0)	
Tumor grade, N (%)					
1	18 (7.8)	4 (5.7)	1 (1.9)	2 (2.9)	0.01
2	93 (40.1)	25 (35.7)	20 (37.7)	17 (25.0)	
3	75 (32.3)	28 (40.0)	25 (47.2)	38 (55.9)	
Elevated tumor markers (%)					
Preoperative CA 15-3	48.1	42.8	26.0	33.3	
RelapseCA 15-3	44.5	33.3	28.9	38.8	0.11
Preoperative CEA	44.3	28.5	43.4	14.3	
Relapse CEA	60.8	54.7	51.1	36.0	
Tumor markers, median (range)					
Preoperative CA 15-3 (U/mL)	29.9 (6.5-798.5)	25.2 (7.6-2450.0)	22.1 (9.9-3204.0)	25.6 (10.6-887.0)	0.47
Relapse CA 15-3	35.4 (8.2-2455.0)	27.9 (8.5-317.1)	26.5 (8.5-114.4)	40.1(10.1-417.4)	
Preoperative CEA (ng/mL)	2.6 (0.4-61.5)	2.6 (0.2-163.1)	2.8 (0.7-206.7)	1.3 (0.3-11.8)	0.001
Relapse CEA	4.3 (0.6-304.8)	4.8 (0.7-84.3)	3.0 (0.6-145.5)	2.4 (0.9-15.3)	

*Other breast, intraabdominal, suprarenal, skin metastasis
**Mucinous, metaplastic, medullary, neuroendocrine, invasive apocrine, invasive papillary, adenosquamous

tients with increased CA15-3 levels either in preoperatively or upon relapse was lower in the HER-2 overexpressing group as compared to the other groups but without statistical significance (p=0.11 and p=0.20, respectively) (Table 4).

Preoperative CEA levels were increased in 44.3% of the patients in luminal A, in 28.5% of the patients in luminal B, in 43.4% of the patients in HER-2 overexpressing, and in 14.3% of the patients in triple-negative groups. In the subgroups, the rates of the patients with elevated CEA levels upon relapse were 60.8, 54.7, 51.1, and 36.0% in luminal A, luminal B, HER-2 overexpressing and triple-negative, respectively. Preoperative CEA levels were within normal range in 85.7% of the patients in the triple-negative group, being signicantly lower (p=0.026) than the non-triple negative groups. The number of patients with increased CEA levels upon relapse was significanly higher in luminal A group (p=0.02) as compared to the non-luminal groups. Likewise, the rate of patients with normal CEA levels upon relapse was statistically significantly lower in the triple-negative group as compared to the non-triple negative groups (p=0.005) (Table 5).

Discussion

Despite their low sensitivity, CEA and CA 15-3 are routinely used as tumor markers in breast cancer. Studies reported that high CEA level at the time of diagnosis is a negative prognostic factor

Table 4. Preoperative and CA 15-3 at relapse according to subgroups

Elevated tumor markers	*Luminal A N=252*	*Luminal B N=70*	*HER-2 overexpressing N=53*	*Triple negative N=68*	*p-value**	*p-value***
Preoperative CA 15-3 (%)	48.1	42.8	26.0	33.3	0.09	0.11
Relapse CA 15-3 (%)	44.5	33.3	28.9	38.8	0.09	0.20

* luminal A group as compared to the non-luminal groups
** HER-2 overexpressing group as compared to the other groups

Table 5. Preoperative and CEA at relapse according to subgroups

Elevated tumor markers	*Luminal A N=252*	*Luminal B N=70*	*HER-2 overexpressing N=53*	*Triple negative N=68*	*p-value**	*p-value***
Preoperative CEA (%)	44.3	28.5	43.4	14.3	0.026	0.08
Relapse CEA (%)	60.8	54.7	51.1	36.0	0.005	0.02

* triple-negative group as compared to the non-triple negative groups
** luminal A group as compared to the non-luminal groups

and is associated with disease stage [19,20]. In the long-term prospective study conducted by Guadagni et al., it was found that CEA level was increased in 15.0% and CA 15.3 level was increased in 39.6% of the patients. In the above-mentioned study, CEA and CA 15.3 were elevated in 37.7 and 73.6% of the patients, respectively, that developed metastasis during follow up [21].

A study consisting of 1046 breast cancer patients reported that increased preoperative levels of CEA and CA 15-3 were associated with early mortality and that both tumor markers were increased on relapse, CA 15-3 elevation being more significant [22]. In a study that analyzed the relationship between increasing tumor markers in breast cancer with clinicopathologic parameters, it was found in 740 patients that the median preoperative CEA and CA 15-3 levels were statistically correlated with tumor mass, number of metastatic lymph node and stage of disease. In the same study, there was no significant relationship with ER, PR and HER-2 status [10].

Although molecular subgroups of breast cancer are identified by gene expression analyses by using DNA microarray technique, in recent years immunohistochemical markers are used instead of DNA microarray technique to identify the subgroups of breast cancer [23]. Subgroups have been identified in order to possibly explain the variable clinical behavior of breast cancer and relevant research has shown that patients in the different subgroups differed in age, metastatic patterns, prognostic factors and survival outcomes [3,23].

No clear data are to be found in the literature showing tumor markers variations among the subgroups in metastatic breast cancer. A study conducted by Dede et al. comprising breast cancer patients that were non-metastatic at the time of diagnosis compared the triple-negative subgroup with non-triple negative subgroups in terms of tumor markers at the time of diagnosis and after development of metastasis. It was found that CEA (2.5 ± 5.9 vs 4.0 ±16.4, respectively; p = 0.35) and CA 15-3 (23.7 ± 14.6 vs 37.1 ± 117, respectively; p = 0.021) levels were lower in the triple-negative group at the time of diagnosis as compared to the non-triple negative groups. Moreover, CEA (3.2 ± 3.8 and 29.6 ± 106.4, respectively; p= 0.022) and CA 15-3 (46.9 ± 46.3 and 203.2 ± 534 respectively; p= 0.008) levels were significantly lower in the triple-negative group also upon relapse [24]. In the present study, the number of patients with elevated CEA level, both at the time of diagnosis and upon relapse, was statistically significantly higher in the luminal A group. CEA levels remained within normal range upon relapse in more patients in the triple-negative group, and the difference was statistically significant (p=0.005). However, no difference was found between the groups in terms of the number of patients with elevated CA 15-3 levels either at the time of diagnosis or upon relapse.

Our study has shown that there are differences in tumor marker elevations in breast cancer subgroups as well as other kinds of differences. Triple-negative group is generally known as a group with a poor prognosis and in our study less elevations of tumor markers at relapse were found in this group when compared to luminal groups. This makes us think that tumor markers are of little help during follow up for timely detection of relapse in the triple negative group. CEA level monitoring, on the other hand, can be useful in identifying early relapses in the luminal A group. This retrospective study requires further prospective confirmative cohort studies.

References

1. Wang Y, Klijn JG, Zhang Y et al. Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer. Lancet 2005;365:671-679.
2. van de Vijver MJ, He YD, van't Veer LJ et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002;347:1999-2009.
3. Perou CM, Sorlie T, Eisen MB et al. Molecular portraits of human breast tumours. Nature 2000;406:747-752.
4. Pedraza V, Gomez-Capilla JA, Escaramis G et al. Gene expression signatures in breast cancer distinguish phenotype characteristics, histologic subtypes, and tumor invasiveness. Cancer 2010;116:486-496.
5. Blows FM, Driver KE, Schmidt MK et al. Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: a collaborative analysis of data for 10,159 cases from 12 studies. PLoS Med 2010;7:e1000279.
6. Sorlie T, Perou CM, Tibshirani R et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001;98:10869-10874.
7. Aksu G, Duman C, Gurbuz Y et al. Correlation between c-erbB2 expression, lymphovascular invasion and other biological and clinical prognostic factors and preoperative tumor markers in patients with early-stage and locally advanced breast cancer. J BUON 2011; 16:52-57.
8. Kesisis G, Kontovinis LF, Gennatas K et al. Biological markers in breast cancer prognosis and treatment. J BUON 2010; 15:447-454.
9. Berruti A, Tampellini M, Torta M, Buniva T, Gorzegno G, Dogliotti L. Prognostic value in predicting overall survival of two mucinous markers: CA 15-3 and CA 125 in breast cancer patients at first relapse of disease. Eur J Cancer 1994;30A:2082-2084.
10. Park BW, Oh JW, Kim JH, Park SH, Kim KS, Lee KS. Preoperative CA 15-3 and CEA serum levels as predictor for breast cancer outcomes. Ann Oncol 2008;19:675-681.
11. Canizares F, Sola J, Perez M et al. Preoperative values of CA 15-3 and CEA as prognostic factors in breast cancer: a multivariate analysis. Tumour Biol 2001;22:273-281.
12. Gion M, Boracchi P, Dittadi R et al. Prognostic role of serum CA15.3 in 362 node-negative breast cancers. An old player for a new game. Eur J Cancer 2002;38:1181-1188.
13. Molina R, Filella X, Alicarte J et al. Prospective evaluation of CEA and CA 15.3 in patients with locoregional breast cancer. Anticancer Res 2003;23:1035-1041.
14. Mughal AW, Hortobagyi GN, Fritsche HA, Buzdar AU, Yap HY, Blumenschein GR. Serial plasma carcinoembryonic antigen measurements during treatment of metastatic breast cancer. JAMA 1983;249:1881-1886.
15. Molina R, Zanon G, Filella X et al. Use of serial carcinoembryonic antigen and 15.3 assays in detecting relapses in breast cancer patients. Breast Cancer Res Treat 1995; 36:44-48.
16. Ballesta AM, Molina R, Filella X, Jo J, Gimenez N. Carcinoembryonic antigen in staging and follow-up of patients with solid tumors. Tumour Biol 1995;16:32-41.
17. Jezersek B, Cervek J, Rudolf Z, Novakovic S. Clinical evaluation of potential usefulness of CEA, CA 15-3, and MCA in follow-up of breast cancer patients. Cancer Lett 1996;110:137-144.
18. Robertson JF, Jaeger W, Syzmendera JJ et al. The objective measurement of remission and progression in metastatic breast cancer by use of serum tumour markers. European Group for Serum Tumour Markers in Breast Cancer. Eur J Cancer 1999;35:47-53.
19. Gaglia P, Caldarola B, Bussone R et al. Prognostic value of CEA and ferritin assay in breast cancer: a multivariate analysis. Eur J Cancer Clin Oncol 1988;24:1151-1155.
20. Safi F, Kohler I, Rottinger E, Suhr P, Beger HG. Comparison of CA 15-3 and CEA in diagnosis and monitoring of breast cancer. Int J Biol Markers 1989;4:207-214.
21. Guadagni F, Ferroni P, Carlini S et al. A re-evaluation of carcinoembryonic antigen (CEA) as a serum marker for breast cancer: a prospective longitudinal study. Clin Cancer Res 2001;7:2357-2362.
22. Ebeling FG, Stieber P, Untch M et al. Serum CEA and CA 15-3 as prognostic factors in primary breast cancer. Br J Cancer 2002;86:1217-1222.
23. Carey LA, Perou CM, Livacy CA et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 2006; 295:2492-502.
24. Dede DS, Aksoy S, Bulut N et al. Comparison of serum levels of CEA and CA-15-3 in triple-negative breast cancer at the time of metastases and serum levels at the time of first diagnosis. J Clin Oncol 2009;27(Suppl): e12017 (abstr).