Relationship between Preoperative Serum Markers CA 15-3 and CEA and Relapse of the Disease in Elderly (>65 years) Women with Breast Cancer*

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Abstract. *This study investigated whether preoperative carcinoma-associated antigen (CA) 15-3 and carcinoembryonic antigen (CEA) serum levels are predictive markers of reduced diseas-free (DF) survival in women with breast cancer (BC) who have undergone curative surgery A series of 363 consecutive postmenopausal women (median age 63 years, range 47-89 years) with pT1-2, N0-1 and M0 BC who underwent curative surgery and were followed-up for at least 36 months after lumpectomy or mastectomy were reviewed retrospectively. Two groups of patients were considered: Group 1 (age 47-64 years), 203 (55.9%) patients; Group 2 (age >64 years), 160 (44.1%) patients. None of the parameters (age, size of the tumour, CA 15-3 and CEA baseline serum levels, ER and PgR rate, MIB-1 labelling index) differed between the groups. During follow-up (36-60 months) 62 (17.1%) patients developed relapse (DR) of the disease (41 and 21 among Groups 1 and 2, respectively), while 301 (82.9%) were DF. The differences were as follows (DF vs. DR): Group 1: CA 15-3 (25.0±11.4 vs. 31.4±14.6 U/l; p=0.003) and CEA serum levels (5.7±4.8 vs. 7.4±6.4 ng/ml; p=0.048). Group 2: CA 15-3 (27.9±13.2 vs. 20.4±6.5 U/l; p=0.012) and CEA serum levels (6.6±5.2 vs. 3.7±2.5 ng/ml; p=0.013). Surprisingly, in the subgroup of patients aged >65 years who developed relapse, both CA 15-3 and CEA baseline serum levels were lower than in the subgroup of DF patients. In conclusion, although serum tumour markers levels may be useful during follow-up, their baseline levels are not useful in predicting relapse in elderly patients with BC.*

Breast cancer (BC) is the most frequently occurring cancer in women and continues to be the most common fatal cancer together with those of the lung, bronchus and colorectum (1). Patients with BC may develop progression or recurrence of the disease, which may ultimately cause them to die, although there are a number of imaging studies and serum tumour markers available that may be potentially useful during their follow-up (2, 3). Tumour markers are substances associated with malignant processes and can be found in cancerous tissues, and in other tissues (*i.e.* lymph nodes) colonized by the primary malignant cells, as well as in some biologic fluids (*i.e.* pleural and peritoneal fluids) that are also usually detected in serum depending on the nature and evolution of the tumour (4). Several serum tumour markers have been proposed to indicate the presence and future behaviour of BC, especially carcinoma-associated antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA) (5, 6).

The aim of this study was to investigate whether preoperative CA 15-3 and CEA serum levels are useful predictive markers of patients who may have a shorter disease free survival after curative surgery in postmenopausal women with BC.

Patients and Methods

Charts from a series of 363 consecutive postmenopausal women (median age 63 years, range 47-89 years) with pT1-2, N0-1, M0 BC who underwent curative surgery and were followed-up for at least 36 months after lumpectomy or mastectomy were reviewed retrospectively. Patients with pT3-4 BC, as well as those who have undergone adjuvant chemotherapy, were excluded from the study. Two groups of women were considered: Group 1 (age 47-64 years),

Table I. *Parameters considered in the overall patient population, differences between the two groups considered and p-value.*

Parameters	Overall	Group 1	Group 2	*p*-Value
Number of patients	363	203	160	-
Age (years)	60.5±12.8	51.1±7.7	72.4±6.4	-
Size (mm)	21.3±9.8	20.2±8.9	22.8±10.6	0.186
CA 15-5 (U/ml)	26.3±15.5	26.1±12.2	26.5±12.9	0.874
CEA (ng/ml)	6.2±5.1	6.3±5.2	6.2±5.1	0.824
MIB-1	21.7±12.8	20.8±12.7	22.8±12.9	0.421
ER	60.0±16.5	60.9±16.6	58.8±16.3	0.535
PgR	54.7±17.6	56.6±17.3	52.3±17.6	0.216

Table II. *Differences between disease-free patients and those with relapse in each group and relative p-value.*

Parameters	Disease-free	Relapse	*p*-Value
Age <65 years			
No. of patients	162	41	-
Age (years)	51.4±7.9	49.7±6.8	0.208
Size (mm)	19.4±9.2	23.3±7.3	0.013
CA 15-5 (U/ml)	25.0±11.4	31.4±14.6	0.003
CEA (ng/ml)	5.7±4.8	7.4±6.5	0.048
MIB-1	21.0±13.4	20.2±9.5	0.719
ER	59.4±17.4	66.8±11.2	0.010
PgR	56.0±17.4	59.1±16.9	0.307
Age >64 years			
No. of patients	139	21	-
Age (years)	72.6±6.6	71.3±4.4	0.384
Size (mm)	22.3±11.0	26.6±7.2	0.085
CA 15-5 (U/ml)	27.9±13.2	20.4±6.5	0.012
CEA (ng/ml)	6.6±5.2	3.7±2.5	0.013
MIB-1	22.3±13.1	26.3±11.1	0.186
ER	58.1±16.6	62.2±12.2	0.279
PgR	52.5±16.9	50.0±21.3	0.543

203 (55.9%) patients and Group 2 (age >64 years), 160 (44.1%) patients. CEA and CA 15-3 serum levels were measured preoperatively in all patients, and the tissue removed during surgery was tested for the presence of oestrogen (ER) and progesterone (PgR) receptors and the mindbomb homolog 1 (MIB-1), a monoclonal antibody against the Ki-67 antigen encoded by the *MKI67* gene and expressed in all proliferating cells. In accordance with the American Joint Committee on Cancer (AJCC), tumour size (pT) was defined as the maximum diameter measured by the pathologist, and involvement of the lymph nodes (pN1) was confirmed histologically (7). Prior to surgery, the presence of distant metastases was excluded by liver ultrasound, standard chest X-ray and whole body bone scintigraphy. Informed consent was obtained from all participants alive at the time of the retrospective study in accordance with Institutional Review Board approval.

The following parameters were considered: patient age, tumour size, CA 15-3 and CEA baseline serum levels, ER and PgR levels and MIB-1 labelling index. CEA and CA 15-3 levels were determined by automated testing using a two-site enzyme-linked immunosorbent assay (ELISA, monoclonal antibody). The manufacturer's recommended cut-off limit of 10 ng/ml (CEA) and 30 U/ml (CA 15-3) was used, as previously described (3, 6). Both ER and PgR were assayed using a quantitative standard immunoenzymatic method, and results were expressed as percentage of positivity in the overall cell population. Immunostaining of Ki-67 antigen was performed using the MIB-1 monoclonal antibody by a microwave antigen retrieval technique, and the MIB-1 labelling index was expressed as a percentage of positive cells.

The resulting data are expressed as mean±standard deviation (SD). The Pearson's correlation coefficient (R) calculation was used to evaluate the linear relationship between pairs of variables, while differences between means were tested by unpaired Student's *t*-test. A value of $p < 0.05$ was considered to be statistically significant.

Results

None of the parameters differed significantly (*p*=not significant [NS]) between groups (Table I). There was a strong relationship between ER and PgR (R=0.52, *p*<0.001), while a weak relationship between CA 15-3 and CEA (R=0.19, *p*=0.007) was found (Figure 1). During follow-up (36-60 months) 62 (17.1%) patients developed relapse (DR) of the disease (41 and 21 among Groups 1 and 2,

respectively), while 301 (82.9%) were disease-free (DF). As expected, the tumour size (DF *vs*. DR) was smaller both in Group 1 (19.4±9.2 *vs*. 23.3 *vs*. 7.3 mm; *p*=0.013) and Group 2 (22.3±11.0 *vs*. 26.6±7.2 mm: *p*=0.085).

The results are reported in Table II and the statistically significant differences were as followings (DF *vs*. DR): Group 1: CA 15-3 (25.0±11.4 *vs*. 31.4±14.6 U/l; *p*=0.003) and CEA serum levels (5.7±4.8 *vs*. 7.4±6.4 ng/ml; *p*=0.048). Group 2: CA 15-3 (27.9±13.2 *vs*. 20.4±6.5 U/l; *p*=0.012) and CEA serum levels (6.6±5.2 *vs*. 3.7±2.5 ng/ml; *p*=0.013).

Discussion

Breast cancer is a progressive disease and small tumours are most likely to occur in the early stages of the disease and indicate a better outcome and a lower risk of recurrences (8). However, despite advances in the diagnosis, staging, and therapeutic approaches achieved over the past 15 years, BC remains one of the leading causes of death in women over the age of 50 (4, 9). The overall estimated number of new BCs in the USA in 2009 was 194,000, accounting for about 27% of cases of cancer in women (1). Several tumour markers have been applied in the diagnosis and long-term follow-up of all cancer patients, although their role is not well established and the usefulness of their measurements is still under discussion (4, 10). CA 15-3 and CEA represent the most common serum tumour markers used in patients with BC, although their value when used in serial observations remains
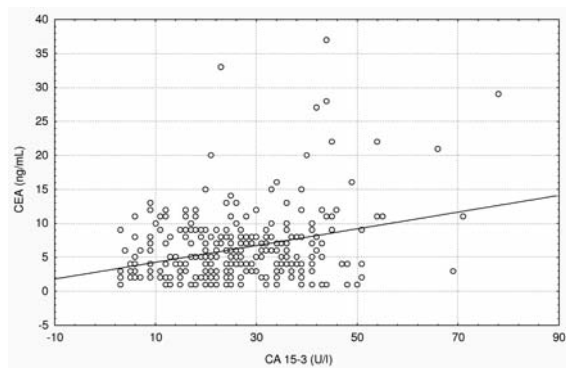
Figure 1. *Relationship between CA 15-3 and CEA serum levels.*

unclear (11, 12). Despite poor prognosis associated with initially high values of CA 15-3 and CEA, their determination in the initial evaluation of patients with BC is suggested as useful in some studies (13).

The sensitivity of CEA in detecting malignancy in both early and advanced BC has been shown to be low when compared with other serum tumour markers, and measurement of CEA together with other serum markers only lead to a slight increase in sensitivity (14). In a retrospective analysis of 784 recurrences of BC, only 35% of patients had an increase of CA 15-3, and treatment planning was therefore not affected by CA 15-3 increase, and survival benefit of marker testing remained undeterminable (15). The combination of both CA 15-3 and CEA may increase the diagnostic accuracy in metastatic disease (16). In contrast, measurement of serum tumour markers was not recommended by the American Society of Clinical Oncology panel for routine BC follow-up (17). Normally, high preoperative serum marker levels are associated with advanced disease and may reflect tumour burden (18). Surprisingly, this study showed that in the subgroup of patients aged >65 years who developed relapse, both CA 15-3 and CEA baseline serum levels were lower than in the subgroup of DF patients. Also studies reported by laboratory centre conclude that the biomarkers are poorly predictive of locoregional recurrences (19).

Conclusion

These results confirm the relationship between CA 15-3 and CEA baseline serum levels in postmenopausal patients with BC, independent of both age and tumour size. Measurement of serum tumour markers may be useful in detecting metastases during follow-up, but CA 15-3 and CEA baseline levels should not be considered as a prognostic factor in predicting relapse in elderly patients with BC.

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