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CA15-3 Assay Contribution in the Management of Breast Cancer: Study of 177 Cases

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Abstract **Original Research Article**

Introduction: Breast cancer is the leading cause of cancer mortality in women worldwide. CA15-3 is the most widely used serum marker in this cancer. The aim of this study is to investigate the CA15-3 assay in breast cancer and its correlation with classical prognostic factors for the disease, as well as with the post-therapeutic evolution of patients. ***Materials and Methods:*** This is a retrospective study, carried out at the Clinical Biochemistry Laboratory of the Tangier university hospital center, involving 177 patients treated at the Tangier Oncology Center, having benefited from a CA15-3 assay according to the ELFA (Enzyme Linked Fluorescent Assay) immunoassay technique, with a threshold value of 30U/ml, as part of their therapeutic management, for a period of 10 months. ***Results:*** A statically significant correlation was found between the marker's level and TNM classification, the expression of hormonal receptors for estrogen (ER) and for progesterone (RP). The high value of CA15-3 is correlated with the number and location of metastatic sites, and also with an unfavourable outcome. Furthermore, monitoring and post-therapeutic evaluation of patients during the metastatic phase, using biomarker kinetics, shows that an increase in biomarker levels relative to the initial value correlates with radiological progression of metastasis and therefore with the advancement of disease. ***Conclusion:*** This study supports the interest of CA15-3 assay in the post-treatment follow-up and in the prognostic evaluation of breast cancer patients.

Keywords: CA15-3, Serum marker, Breast cancer, Metastasis, biomarker kinetics.

INTRODUCTION

Breast cancer is the most common malignant tumor in women, it is the leading cause of cancer mortality among women worldwide and therefore represents a major public health problem for all countries [1, 2]. Breast cancer cells are most often involved in the production of carbohydrate antigen 15-3 (CA15-3), which is the serum marker most used in the management of breast cancer [3].

CA15-3 is a transmembrane glycoprotein circulating in the blood, belonging to the mucin family, derived from polymorphic epithelial mucin (PEM) and encoded by the MUC1 gene which is involved in cell adhesion mechanisms, thus defined by its immunoreactivity with two monoclonal antibodies which are 115 D8, directed against the membrane of human milk fat globule and DF3, directed against the membrane of human breast cancer cells [4, 5]. It is expressed on the surface of different types of normal epithelial cells, but aberrantly overexpressed by tumor cells in breast cancer [6].

The aim of this study will be to investigate the CA15-3 assay in breast cancer and its correlation with clinical, histological, radiological and prognostic features, as well as with the post-therapeutic evolution of cases.

MATERIALS AND METHODS

This is a retrospective study, carried out in the Clinical Biochemistry laboratory of Tangier University Hospital, involving 177 patients treated at the Tangier Oncology Center, having benefited from a CA15- 3 assay as part of their therapeutic care, this during the period from September 15, 2021 to June 15, 2022.

Inclusion Criteria:

Patients with histologically confirmed primary breast cancer, having performed one or more CA15-3 assays in our laboratory.

Exclusion Criteria:

We excluded from our study male patients, patients with secondary breast cancer, those in whom we did not find enough information and exploitable data and those who had not performed the CA15-3 assay in our laboratory.

Data Collection

All our data were collected from the computer system "e-labs LIMS: Laboratory Management System" for CA15-3 assay results, and from the "Enova health system" for data from our patients' medical records, then these elements are processed in the form of an Excel table while respecting anonymity.

Laboratory Technology

∞ **Sample Collection and Processing:**

Blood samples for the CA15-3 assay were collected from peripheral venous blood in dry tubes, in our sampling unit, while complying with sampling conditions. Whole blood collected to obtain serum was centrifuged at 3000 x g for 10 minutes at +4°C, immediately after coagulation. Serum was stored at 2-8°C in stoppered tubes for a maximum of 48 hours, with freezing at -25°C when longer storage was required, but not exceeding 2 months.

∞ **Equipment: VIDAS® Biomérieux Automaton**

∞ **Principle of the Procedure:**

Based on the ELFA (Enzyme Linked Fluorescent Assay) reaction, the principle combines a 2-step "sandwich" enzyme-linked immunosorbent assay with final fluorescence detection (ELFA). The receptacle (SPR®) serves as the solid phase and pipetting device for the assay, and the reagents are ready-to-use and predispensed in sealed strips. All assay steps are performed automatically by the instrument, allowing the reaction medium to flow in and out of the SPR several times, enabling the 115D8 monoclonal antibody bound to the inner wall of the SPR to capture reactive antigenic determinants present in the sample. The unbound components are removed in the washing steps and the alkaline phosphatase (PAL)-labeled DF3 monoclonal antibody is then incubated in the SPR where it binds to the DF3 reactive antigenic determinants, then the unbound conjugate is subsequently removed in the washing steps. Finally, in the last detection step, the substrate (4-Methyl-umbelliferyl phosphate) moves in and out of the SPR, enabling the conjugated enzyme to catalyze the hydrolysis of this substrate into a fluorescent product (4-Methyl-umbelliferone), whose fluorescence is measured at 450 nm and its intensity is proportional to the concentration of CA15-3 antigenic determinants present in the sample.

Once the test has been completed, the results are automatically calculated using calibration curves stored by the instrument. This calculation appears on the results sheet and concentrations are expressed in U/ml.

∞ **Interpretation of Results**: According to manufacturer's recommendations

The analytical methods used to measure markers are validated by the reagents' original laboratories and verified on the laboratory's automatons. Depending on the method used, the CA15-3 marker level is considered normal if it is less than 30 U/ml. Samples with CA15-3 titers > 400 U/ml are reanalyzed after dilution to a maximum of 1/10 (1 volume of sample and 9 volumes of CA15-3 diluent) and the result is multiplied by the dilution factor to obtain the CA15-3 concentration of the sample tested.

Statistical Analysis

All analyses were performed with IBM SPSS V21. Descriptive statistics were presented as means and medians for continuous variables, and as frequencies and percentages for categorical variables. Samples were compared using the non-parametric Mann-Whitney test. Correlation was performed using the Spearman test. A p-value <0.05 was accepted as statistically significant.

RESULTS

Of the 177 cases, 41.25% had a positive initial CA15-3 level (≥30U/ml) and 58.75% had a negative assay (<30U/ml). Patients' initial CA15-3 levels ranged from 4.31 to 8000U/ml, with a median value of 23.61U/ml.

The mean age of patients was 52,20 ± 11,48 years (29-85). 55.4% were still genitally active, while 44.6% were menopausal. The initial tumor site was the left breast in 56.5% of cases and the right breast in 43.5%. Histological type was dominated by invasive ductal carcinoma (IDC), which accounted for 93.8% of cases, while invasive lobular carcinoma (ILC) was found in only 3.4% of cases, and other types in 2.8%. Distant metastases (M+) were found in 104 of the 162 patients whose metastatic status was known, of whom 60.6% had a positive marker level, while 40.4% were false negatives. 7% were stage T1, 35% stage T2, 12% stage T3 and 46% were stage T4. A further 18.4% had no lymph node involvement (N=0), while 80.6% had lymph node involvement (N ≥1). The number of metastatic sites was single (< 2sites) in 26% of cases and multiple (≥ 2sites) in 74%.

The location of metastases was bone in 79.8%, pleuropulmonary in 68.25%, liver in 49%, central nervous system in 14.4%, mediastinum in 7.7%, peritoneal cavity in 4.8%, ovary, skin and left adrenal gland in one case respectively. Concerning the SBR grade, 3.75% of cases were stage I, 43% stage II and

53.25% stage III. Estrogen receptors (ER) were expressed in 67.8% of cases, progesterone receptors (PR) in 91% and HER2 receptors in 23.4%. The evolution was marked by the absence of transition to the metastatic phase in 14% of cases. It was marked by the regression of metastatic extension in 18% of cases and by the metastatic progression in 22.6% of cases. Homolateral recurrence was observed in 1.7% of cases and contralateral recurrence in 2.8%. One patient died and another was lost to follow-up, while 39.6% of cases were under evaluation.

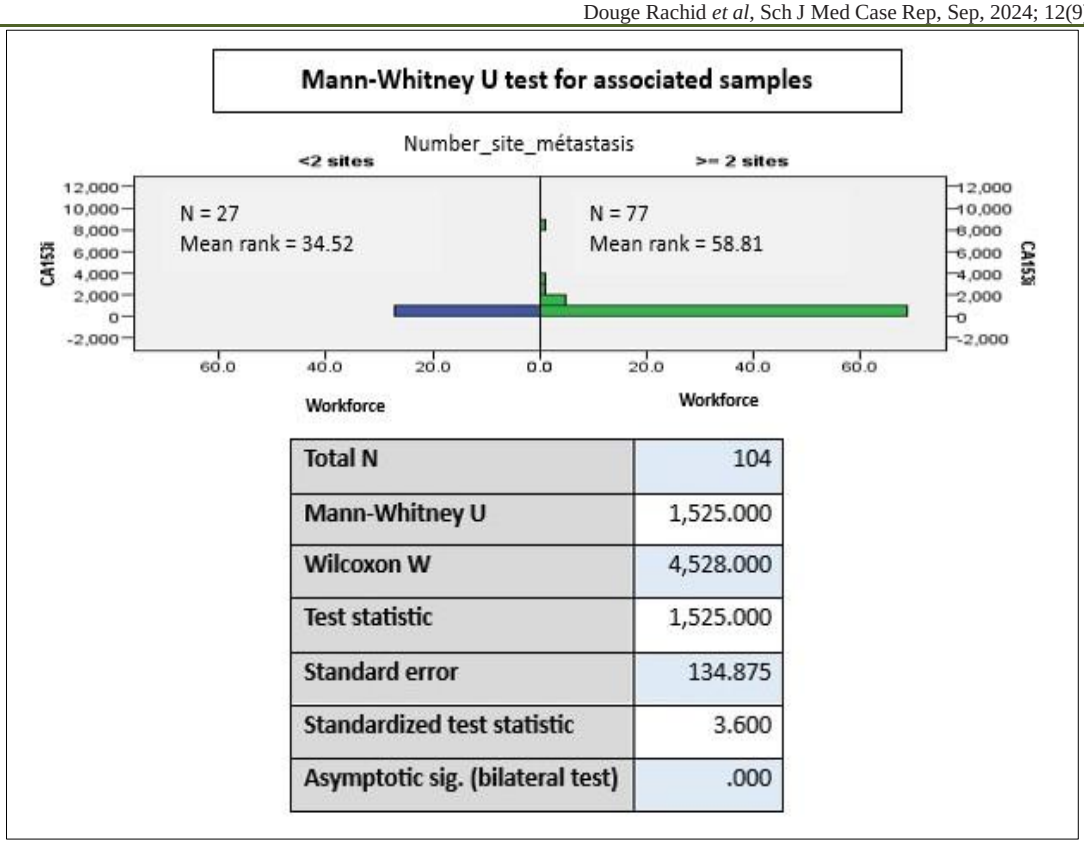
A statically significant difference in CA15-3 levels was found, according to the clinical TNM classification and according to the expression of Estrogen Receptors (ER) and Progesterone Receptors (PR), with ($p < 0.001$) respectively for T, N, M and ER and ($p = 0.021$) for PR. However, no significant correlation was detected between marker levels and patients' age, menopause, initial tumor location, SBR grade and HER2 hormone receptor. [Table1]

Elevated CA15-3 levels were observed in patients with multiple metastatic sites (≥2) compared to those with a single location ($p < 0.001$) [Figure1]. Also, the marker level is elevated in some metastatic locations, notably bone, pleuropulmonary and liver, with ($p < 0.001$) respectively, while metastatic location in the central nervous system (CNS) did not correlate with marker elevation [Table2].

In all cases, an elevated initial CA15-3 level correlated with an unfavorable outcome ($p<0.001$) [Figure2]. Furthermore, in cases with metastatic disease, an increase greater than 25% in the serum marker level during post-therapeutic follow-up compared with the initial level was correlated in 71.4% of cases with radiological progression of the metastasis, whereas a decrease more than 25% in this level compared with the initial reference value was associated in 76.6% of cases with a regression in the metastatic evolution of the disease [Figure3].

Table 1: Correlation of CA 15-3 with classic prognostic factors for the initial disease

Parameters	Number	%	CA15-3 < 30U/ml (%)	CA15-3 ≥ 30U/ml (%)	P value
Age					
≤ 50 years	80	45,2	48 (60)	32 (40)	0,868
> 50 years	97	54,8	57 (58,8)	40 (41,2)	
Menopause					
Yes	79	44,6	46 (58,2)	33 (41,8)	0,79
No	98	55,4	59 (60,2)	39 (39,8)	
Location of initial tumor					
Right breast	77	43,5	49 (63,6)	28 (36,4)	0,304
Left breast	100	56,5	56 (56)	44 (44)	
Histological type					
IDC	166	93,8			
Other types	11	6,2			
Clinical TNM classification					
T					
T1-T2	68	42	53 (77,9)	15 (22,1)	< 0,001
T3-T4	94	58	47 (50)	47 (50)	
N					
N = 0	30	18,4	27 (90)	3 (10)	< 0,001
N ≥ 1	133	81,6	74 (55,6)	59 (44,4)	
M					
M-	50	32,5	43 (86)	7 (14)	< 0,001
M+	104	67,5	41 (39,4)	63 (60,6)	
SBR stage					
I & II	75	46,9	45 (60)	30(40)	0,761
III	85	53,1	53 (62,4)	32 (37,6)	
Hormone receptors					
ER					
ER-	55	32,2	45 (81,8)	10 (18,2)	< 0,001
ER+	116	67,8	59 (50,9)	57 (49,1)	
PR					
PR-	80	46,8	56 (70)	24 (30)	0,02
PR+	91	53,2	48 (52,7)	43 (47,3)	
HER2					
HER2-	131	76,6	76 (58)	55 (42)	0,139
HER2+	40	23,4	28 (70)	12 (30)	



Total N	104
Mann-Whitney U	1,525.000
Wilcoxon W	4,528.000
Test statistic	1,525.000
Standard error	134.875
Standardized test statistic	3.600
Asymptotic sig. (bilateral test)	.000

Figure 1: Difference between initial CA15-3 level in single metastatic locations and in multiple locations.

Table 2: CA15-3 levels by metastatic location

Localization of metastases	Number	%	CA15-3 < 30U/ml (%)	CA15-3 ≥ 30U/ml (%)	P value
Bone	83	79,8	27 (32,5)	56 (67,5)	< 0,001
Hepatic	51	49	19 (37,7)	32 (62,7)	< 0,001
Pleuropulmonary	71	68,25	23 (32,4)	48 (67,6)	< 0,001
Cerebral	15	14,4	9 (60)	6 (40)	0,477
Other	16	15,4	4 (25)	12 (75)	

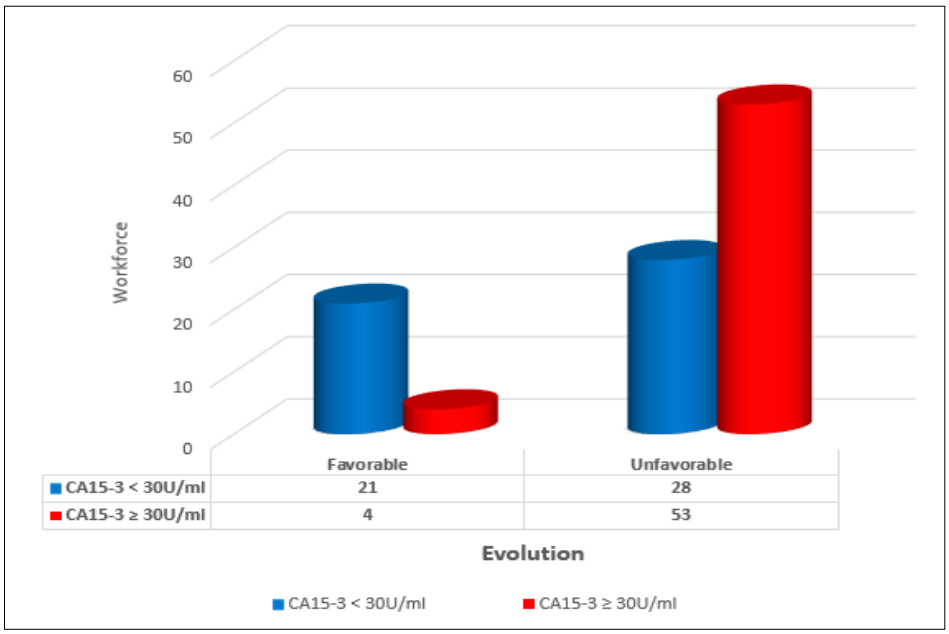
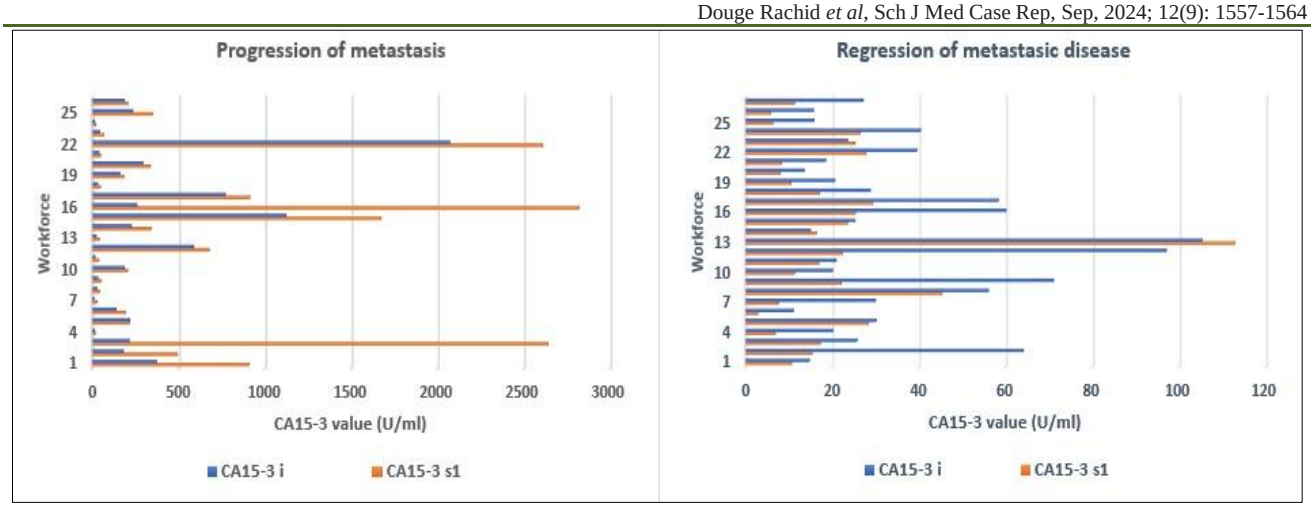


Figure 2: Evolution of all cases according to the initial CA15-3 level



*CA15-3 i: Initial reference value *CA15-3 s1: First assay performed during monitoring

Figure 3: Variations in CA15-3 kinetics according to the post-therapeutic evolution of metastatic cases

DISCUSSION

The retrospective nature of our study represents the main limitation, explaining the absence of a certain amount of data for some cases, yet several conclusions are clear.

Despite the possibility of detecting breast cancer micro-metastasis using CA15-3 assay, whose elevation can precede the onset of clinical and radiological signs by several months, generally 2 to 18 months [7-10], the use of this marker is not recommended for the diagnosis of breast cancer, nor for screening for local and distant recurrence, as has been reported in the literature [8-12]. This is due on the one hand to the lack of proven clinical benefit on survival and quality of life of cases by early detection of subclinical metastasis using the CA15-3 assay [9-14] and on the other hand to the low sensitivity of this marker in the early stage of disease [4-17] and in the detection of single and unifocal metastatic breast cancer relapse [9-19]. Consequently, a sub-threshold CA15-3 level at the time of the initial work-up is not sufficient to rule out the presence of distant metastasis or to exclude the performing of a standard extension work-up [18]. In our study, CA15-3 level was elevated in 61% of patients in the metastatic phase, while 39% were false-negative, which is consistent with the literature, where the sensitivity of the marker varies from 50 to 85% in the metastatic episode [15-21]. This variability can be explained by the heterogeneity of the cases recruited [22], by the multiplicity of threshold values adopted by the authors in the various publications [12-23], but also by the lack of specificity of this marker, an increase of which can be found in some physiological or pathological situations outside any breast cancer pathology, such as pregnancy, liver disease, chronic epigastralgia, hypothyroidism, chronic lung disease, benign ovarian pathologies [24], and also in non-specific inflammatory conditions [19], benign mastopathies and ductal carcinoma in situ (DCIS) [23-25], as well as in some tumour pathologies, notably ovarian, respiratory, hepato-biliary, pancreatic, colorectal and some haematological malignancies [24-27]. However, the sensitivity and specificity of CA15-3 can be increased by its association with other markers, in particular ACE, FTO and PIK3CB [26-28].

The usefulness of assaying this marker is linked to the determination of an initial so-called reference value, which would provide clinicians with an element of comparison in subsequent assessments, that is the study of the marker's kinetics in the same patient rather than the exceeding of a static threshold [13-24]. Admittedly, this initial assay value indicates the degree of vascular supply to the tumour and the possibility of the existence of micro-metastasis, and therefore represents an absolute poor prognostic factor, independently of several parameters as described in numerous studies [29-32], whose elevation should prompt a search for deep metastatic localization [9-24]. In our series, only 16% of patients with a favourable outcome had an elevated initial CA15-3 level, whereas over 65% of cases with an unfavourable outcome had an elevated marker level. Furthermore, variations in the serum marker make it possible to judge the response and efficacy of treatment, particularly in metastatic localizations which are difficult to assess using conventional methods [12-33], knowing well that advanced or metastatic breast cancer is considered to be a chronic disease, whose treatment is essentially palliative, aimed at slowing the progression of metastasis and their clinical symptoms [9-13]. Similarly, the study of CA15-3 kinetics during therapeutic follow-up also has a prognostic value, providing an idea of disease evolution, the occurrence of distant metastasis and recurrences, as well as on disease-free survival and overall survival of cases [4-33]. In fact, according to several studies [2-33], during post-therapeutic follow-up of cases in the metastatic phase, an increase in CA15-3 level of over 25% correlates with metastatic progression and therefore to an advancement of the disease, and conversely, a decrease greater than 25% in the biomarker

level is associated with regression of metastatic disease, which is consistent with the findings of our series.

Moreover, a transient and paradoxical rise in CA15-3 is sometimes noted at the start of treatment, corresponding to the spike effect, which is linked to tumor lysis following apoptosis and necrosis of malignant cells secondary to the effect of treatment [23-34]. This effect is observed in 4.8% of breast cancer cases undergoing chemotherapy [18], and can sometimes be difficult to distinguish from real progression [24]. Although discrepancies between marker kinetics and clinical evolution may be due to this phenomenon, they may also result from a reduction of the initial tumour by the treatment with the occurrence of a new lesion, which justifies recommendations requiring the association of the biomarker with the anamnesis, clinical examination and imaging tests when assessing the therapeutic response in breast cancer [18-34].

CA15-3 concentration reflects the tumor burden of breast cancer, and its elevation appears correlated in several publications with the stage of lesion extension, notably with the size of the initial tumor mass and its inflammation (T), lymph node extension (N) and metastatic dissemination (M) [4-35]. It is also correlated with the expression of hormone receptors, in particular estrogen and progesterone receptors [2-33]. These findings are identical to those found in our study. Nevertheless, according to the results of our series and several publications, marker elevation is not significantly related to patients' age [16-28], menopausal status [4-32], tumour histological type [1-30], histo-pronostic grade (SBR) [5-35] and HER2 status [1-36], but a correlation was found between marker positivity and one or more of these parameters in a few studies. This discordance between the different series means that the marker is devoid of any independent prognostic value in relation to these latter factors.

CA15-3 sensitivity is high in multiple or multivisceral metastatic sites (≥ 2 sites) compared with a single metastatic lesions (< 2 sites) [7-17], and in some preferential locations in particular, bone [16-33], liver [5-19], and lung [9-36]. Furthermore, the sensitivity of the marker is low in other sites including the central nervous system location [5-20]. These results are similar to those of our series. Indeed, the significant and early increase in CA15-3 according to the number and location of metastatic sites is probably due to the fact that the marker's level is related to the size of tumour mass, which is smaller in single metastases and in brain and skin locations, for example, where clinical signs and discovery are earlier than in other deep-seated sites [36].

Measurement of CA15-3 carbohydrate antigen levels is generally based on immunometric assays, but given the existence of sometimes significant inter-laboratory variability and discordance, caused by a difference in assay sensitivity from one technique to another, individual biological monitoring should preferably be carried out using the same assay technique and in the same laboratory [12-37].

CONCLUSION

The serum CA15-3 assay is a useful tool in the management of patients undergoing treatment for breast cancer, particularly in the monitoring of post-therapeutic evolution in the metastatic phase. The marker variations in these treated cases provide precise and early information on the evolutionary meaning of the malignant pathology and on the efficacy of the therapeutic protocol.

Conflicts of Interest: The authors declare that they have no conflict of interest regarding the publication of this paper.

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