

# An individual reference limit of the serum CEA–TPA–CA 15-3 tumor marker panel in the surveillance of asymptomatic women following surgery for primary breast cancer

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**Purpose:** The purpose of this study was to evaluate the combined measurement of serum CEA, TPA, and CA 15-3, using an individual reference limit (IRL), for predicting distant metastases in asymptomatic women following a diagnosis of primary breast cancer.

**Methods:** A total of 231 patients were followed up for a mean of  $5.5 \pm 1.6$  years. An IRL for defining critical changes (CCs) in marker levels was used as a warning signal of pending distant metastases.

**Results:** Sensitivity, specificity, and accuracy of the combined CEA–TPA–CA 15-3 marker panel for predicting patient outcome were 95.2%, 97.8%, and 97.9%, respectively. In all, 19 (8.3%) patients relapsed with a mean lead time to radiological evidence of metastases of  $11.7 \pm 13.8$  months.

**Conclusion:** We concluded that the combined measurement of CA 15-3, CEA, and TPA using an IRL for determining the CC in markers levels is an accurate strategy for predicting outcome during postoperative monitoring of asymptomatic breast cancer patients. Whether the early prediction of metastasis and subsequent administration of therapy impacts on patient outcome should now be the objective of a prospective clinical trial. The marker panel described here could serve as the basis for such a trial.

**Keywords:** breast cancer, postoperative monitoring, serum tumor markers, individual reference limit, early detection of relapses

## Introduction

Although the serial measurement of circulating markers during postoperative monitoring of asymptomatic breast cancer patients can result in the early detection of metastatic disease,<sup>1</sup> the practice is opposed by most American and European expert panels.<sup>2–5</sup> The main reason for this opposition is the absence of high-level evidence demonstrating that measurement of serum markers in this setting has clinical utility, ie, enhances patient outcome or leads to a better quality of life. Despite most published guidelines recommending against the use of markers in the postoperative surveillance of asymptomatic women, many centers continue to perform these tests, especially CA 15-3 and CEA.<sup>6–8</sup> Less frequently measured markers during surveillance include TPA, TPS, and the soluble form of HER2.<sup>1</sup>

Early work showed that measurement of single markers had limited sensitivity and specificity in detecting early metastatic disease following curative surgery for breast cancer.<sup>9–11</sup> More recent data, however, using multiple markers have shown

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increased accuracy for detecting early metastases.<sup>12–14</sup> To further enhance the accuracy for detection of metastases, we investigated an individual reference limit (IRL) as a cutoff point for a panel of three markers, ie, CEA, TPA, and CA 15-3.<sup>15</sup> In this preliminary study, after a mean follow-up of 3.7 years, the sensitivity of the marker panel for detecting metastases was 93% and the specificity was 97.6%.<sup>15</sup> The aim of the present study was to confirm these preliminary findings using a greater number of patients and longer follow-up.

## Materials and methods

### Marker measurement and patient follow-up

From September 2009 to January 2017, 231 consecutively women who had undergone mastectomy for breast cancer and who were disease free were intensively monitored for  $5.5 \pm 1.6$  years (mean  $\pm$  sd; range, 1–7.4 years) with serial serum determination of the marker panel, CA 15-3, CEA, and TPA. Mean age of the patients was 62 years (mean  $\pm$  sd, 9 years; range, 36–84 years). No patient received neo-adjuvant treatment. To date, 19 patients have relapsed. Clinical data relating to 11 survivors from these 19 relapsed patients were updated in December 30, 2017. During follow-up, the marker panel was measured every 3 months. All marker determinations were performed as previously reported.<sup>15</sup> In addition to the serial marker determinations, physical and radiological examinations were performed every 6 months. Laboratory data and instrumental examinations were carried out by personnel blinded to the clinical status of the patients.

### Determination of the IRL for assessing critical change (CC) in marker levels

Since factors such as the presence of concurrent benign disease and woman's age may affect marker levels, we used an IRL for determining the CC signaling the emergence of early metastases. For each disease-free patient, the IRL was calculated using the mean marker concentration  $\pm$  sd of the 5 five consecutive monthly determinations. The IRL was computed as mean  $\pm$  2 sd for CEA and CA 15-3 and mean  $\pm$  3 sd for TPA. The use of 3 rather than 2 sd for TPA was due to the higher analytical and biological variability of TPA compared to CEA and CA

15-3.<sup>16</sup> When the sd of the 5 consecutive monthly determinations was less than 20% of the mean value, the 20% of the mean value was used as sd. To minimize the impact of possible new benign disease or progression of existing disease altering markers levels, the IRL was recalculated every 3 years. Two consecutive values of any of the three markers giving levels higher than the IRL were considered a CC and thus regarded as suspicious of relapse (Table 1). In this situation, a complete instrumental workup was immediately carried out to establish if recurrence(s) was present.

### Radiological examinations

Both at the start and end of the study, all patients underwent skeletal X-ray, bone scintigraphy (BS), liver echography (LE), and abdomen and thoracic computed tomography (AT-CT).<sup>17–19</sup> During follow-up, BS, LE, and AT-CT examinations were carried out in patients suspected of a pending relapse as indicated by clinical symptoms and/or increasing marker level. Patients with positive radiological examinations were investigated as follows: hotspots on the BS with an equivocal interpretation were confirmed by computed tomography (CT) and/or magnetic resonance imaging (MRI); thoracic lesions equivocal by CT were clarified by bronchoscopy and/or cyto/histologic examination; equivocal LE lesions were further investigated by CT or fine needle aspiration cytology; soft tissue involvement was confirmed by cytology and/or histology; and pleural or peritoneal involvement was confirmed by cytology or imaging. In cases where the diagnostic workup was negative or unclear, a full diagnostic clinical and radiological assessment was carried out every 6 months up to 18 months until the uncertainty was resolved. If the diagnostic assessment was found to be negative, the marker warning signal was considered false and such patients returned to standard follow-up with the marker panel. Consistent with current guidelines, yearly mammographic screening was carried out in all patients. All patients provided consent to be postoperatively monitored with the instrumental and laboratory examinations described.

### Determination of lead time (LT)

In relapsed patients, the marker LT was defined as the time from the second of the two consecutive increments of the

**Table 1** Formula for calculation of the IRL and definition of CC of a serum tumor marker panel

Parameter	Definition
IRL	Mean of 5 consecutive monthly values plus 2 sd for CEA and CA 15-3 or 3 sd for TPA; when sd is <20% of mean, 20% of mean is the applied sd
CC	When 2 consecutive values of one or more markers of the panel are higher than IRL measured in two consecutive samples, the latter withdrawn 2–4 weeks following the former. A CC defines a "warning signal"

**Abbreviations:** CC, critical change; IRL, individual reference limit.

first CC to definitive radiological and/or cytohistological diagnosis of metastatic disease. Relapses were categorized as follows: 1) relapses in patients without any ongoing adjuvant (AV) treatment (n=10); 2) relapses in patients who were under prolonged AV hormone therapy (n=2); and 3) relapses in patients who were under prolonged AV treatment that was changed at the time of the CC (n=8). The AV treatment for patients in the last subgroup before and after CC was hormone therapy followed by chemotherapy (CH) in three patients, CH followed by hormone therapy in one patient, a different regimen of CH administered to one patient, and first-line hormone therapy followed by second-line hormone therapy in three patients.

## Statistical analyses

Categorical data were described by frequency (absolute and relative), whereas continuous data were expressed by mean and sd. To evaluate the normality of the LT distribution, the Kolmogorov–Smirnov test was carried out and the comparison between groups (with and without AV treatment, current and previous methodology) was performed by Student's *t*-test (two tailed). Data relating to the marker tests were expressed as percentage of sensitivity and specificity. Sensitivity was computed in relapsed patients as positive results at the test CC (true positives)/the total number of true relapses (true positives plus false negatives). Specificity was computed as the number of negative results in the absence of a CC in marker levels (true negatives) divided by the number of true negatives plus false positives. Accuracy was computed as the number of true-negative results plus true-positive results divided by the total number of results. A positive test (CC) was defined as true- or false-positive test, and a negative test (CC) was defined as true- or false-negative test according to whether it was or was not confirmed by a prolonged clinical-imaging course, respectively. The rate of false “warning signals” per year of follow-up per 100 patients was defined as the ratio between the total number of false warning signals and the number of years a patient was at risk. Finally, a comparison between specificity (first 3 years against the successive 3 years IRL determination) was carried out by the two-proportion *z*-test. Significance was fixed at 0.05. All analyzes, descriptive and inferential, were performed by SPSS v.24 technology.

## Results

### Non-relapsed patients

After a mean follow-up of 64.9 months ( $\pm 19.6$  months, sd), 212 (91.7%) of the 231 patients were apparently free

of distant metastases. In total, 4,763 measurements of CEA-TPA-CA 15-3 were carried out in 212 patients. The AV treatments received by these women and the characteristics of their tumors are summarized in Table 2. The specificity of CEA, TPA, CA 15-3, CEA-CA 15-3, and CEA-TPA-CA 15-3 combination for predicting absence of metastasis was 99.5%, 98.6%, 99.7%, 99.2%, and 97.8%, respectively (Table 3). The rates of false warning signals

**Table 2** Principal characteristics of the 212 studied patients

Characteristics	n	%
Sex		
Male	4	1.9
Female	208	98.1
Surgery		
Total mastectomy	65	30.4
Quadrantectomy	147	69.6
Stage		
0	8	3.8
IA	107	50.4
IB	4	1.9
IIA	59	27.8
IIB	24	11.3
IIIA	5	2.4
IIIB	1	0.5
IIIC	4	1.9
Grade		
1	21	9.9
2	88	41.5
3	99	42
Unknown	14	6.6
ER and PR		
ER-/PR-	35	16.5
ER-/PR+	6	2.8
ER+/PR-	19	9.1
ER+/PR+	129	60.8
Unknown	23	10.8
HER2		
Positive	46	21.6
Negative	83	39.2
Unknown	83	39.2
MIB-1		
>10%	91	42.9
≤10%	63	29.7
Unknown	58	27.4
AV therapy		
CH	4	1.9
HT	17	8
RT	7	3.3
CH-HT	34	16
CH-RT	17	8
HT-RT	39	18.4
CH-HT-RT	75	35.4
None	19	9

**Note:** HER2-positive patients also have received 1–2 years of AV trastuzumab.

**Abbreviations:** AV, adjuvant; CH, chemotherapy; HT, hormone therapy; RT, radiation therapy.

**Table 3** Serum determinations higher than IRL and false warning signals for CEA, TPA, CA 15-3, and CEA-TPA-CA 15-3 combination in the 231 studied patients with a mean follow-up of 64.9 months (range: 12–89 months)

Total blood samples, D=4,763 (couples evaluated =4,314)	CEA (ng/mL)	TPA (U/mL)	CA 15-3 (U/mL)	CEA-CA 15-3 combination	CEA-TPA-CA 15-3 combination
D higher than IRL	118 (2.5%)	343 (7.2%)	70 (1.5%)	188 (3.9%)	531 (11.1%)
FWS (n)	22	59	12	34	93
Specificity (%)	99.5	98.6	99.7	99.2	97.8
FWS per year of F-U per 100 points (n)	1.8	5.1	1.1	2.9	8
Specificity comparison* (P-values)	0.822	0.079 <sup>b</sup>	0.771	0.858	0.438

Notes: \*First 3 years vs the successive 3 years of the postoperative monitoring. <sup>b</sup>98.3%, n=2,568 (2,611–43) vs 99.1%, n=1,687 (1,703–16).

Abbreviations: D, determinations; F-U, follow-up; FWS, false warning signal; IRL, individual reference limit.

per year of follow-up per 100 patients were 1.8, 5.1, 1.1, 2.9, and 8 for CEA, TPA, CA 15-3, CEA-CA 15-3, and CEA-TPA-CA 15-3 combinations, respectively (Table 3).

## Relapsed patients

Of the 231 patients studied, 21 relapses occurred in 19 (8.3%) patients. The AV treatments received by these women and the characteristics of their tumors are summarized in Table 4. In the eight relapsed patients with stage IA, the molecular biological subtype was luminal A (one), non-luminal (one), luminal B (two), ER+ with not determined HER2 (three), and no biological parameters determined (one). Furthermore, the disease-free interval (DFI) was relatively long (167±96 months, mean ± sd). Table 5 lists the DFI, sensitivity, and LT of the marker panel. One of the 19 relapsed patients with skeletal involvement was falsely negative, while for all the remaining 20 relapses, the IRL-CC was the warning signal. No patient had clinical symptoms at the radiological diagnosis of metastases. Two patients relapsed twice. In both of these cases, the first relapse involved liver lesions that were surgically removed. After being apparently disease free for 3 years, one of these patients developed bone involvement, while the other recurred with cerebellum metastasis after 2 years being apparently disease free.

The metastases sites in the other 16 patients were: bone in 5, lung in 2, liver in 2, soft tissues in 5, bone and soft tissues in 1, and bone, lung, and soft tissues in 1 patient. In patients relapsing during AV therapy, sensitivity ranged from 27.3% for CEA or TPA to 90.9% for the CEA-TPA-CA 15-3 combination. The addition of TPA to the CEA-CA 15-3 panel increased the sensitivity from 63.6% to 90.9%. In patients relapsing without AV therapy, sensitivity ranged from 40% for CA 15-3 to 100% for CEA-TPA-CA 15-3. The addition of TPA to the CEA-CA 15-3 panel increased the sensitivity from 80% to 100%. A CC for CEA, TPA, CA 15-3, the CEA-CA 15-3 combination, and the CEA-TPA-CA 15-3 combination occurred in 8, 8, 8, 15, and 20 of the 21 relapses. Therefore,

**Table 4** Principal characteristics of the 19 relapsed patients

Characteristics	n	%
Sex		
Male	1	5.3
Female	18	94.7
Surgery		
Total mastectomy	11	57.9
Quadrantectomy	8	42.1
Stage		
IA	8	42.1
IIA	5	26.3
IIIA	3	15.8
IIIC	2	10.5
IV NED	1	5.3
Grade		
2	6	31.6
3	13	68.4
ER and PR		
ER-/PR-	1	5.3
ER+/PR-	2	10.5
ER+/PR+	15	78.9
Unknown	1	5.3
HER2		
Positive	2	10.5
Negative	11	57.9
Unknown	6	31.6
MIB-1		
>10%	12	63.2
≤10%	3	15.8
Unknown	4	21
AV therapy		
HT	5	26.3
RT	1	5.3
CH-HT	4	21
HT-RT	1	5.3
CH-HT-RT	8	42.1

Abbreviations: AV, adjuvant; CH, chemotherapy; HT, hormone therapy; NED, no evidence of disease; RT, radiation therapy.

in 20 (95.2%) of the 21 relapses, the warning signal from the three markers was the alarm sign for a radiological assessment for possible metastatic disease. Sensitivity ranged from 27.3% for CEA or TPA to 95.2% for CEA-TPA-CA 15-3. The addition of TPA to the CEA-CA 15-3 panel increased the sensitivity from 71.4% to 95.2% (Tables 5 and 6). For

all 21 relapses, the mean  $\pm$  sd LT was 13.7 $\pm$ 15.1 months for the CEA-CA 15-3 combination and 11.7 $\pm$ 13.8 months for the CEA-TPA-CA 15-3 combination. In patients relapsing in the absence of AV therapy, the mean  $\pm$  sd LT was 7 $\pm$ 6.4 months, 8.8 $\pm$ 8.5 months, and 8.5 $\pm$ 8.2 months for CEA, TPA, and CA 15-3, and it was 7.2 $\pm$ 7.1 months and 7.9 $\pm$ 7.1 months for CEA-CA 15-3 and CEA-TPA-CA 15-3, respectively. The difference was significant for CEA and CEA-CA 15-3 association ( $P=0.027$  and  $P=0.041$ , respectively).

In patients who relapsed while receiving AV therapy, the mean  $\pm$  sd LT was 28.7 $\pm$ 27 months, 2.7 $\pm$ 2.1 months, and 15.5 $\pm$ 11.1 months for CEA, TPA, and CA 15-3, whereas it was 21.1 $\pm$ 18.8 months and 15.6 $\pm$ 17.8 months for CEA-CA 15-3 and CEA-TPA-CA 15-3, respectively. In two patients, after having obtained their informed consent, hormone therapy was started at the time of the warning signal from the CEA-TPA-CA 15-3 combination, with negative radiological examinations. When both these relapses were added to the group of eleven relapses in patients receiving

postoperative AV treatment (Table 6), the mean  $\pm$  sd LT became 15.9 $\pm$ 16.1 months (vs 5.2 $\pm$ 5.4 months,  $P=0.052$  for relapses without postoperative AV therapy).

## Survival of patients with metastasis

As of December 2017, 11 (58%) of the 19 relapsed patients were alive. In seven of the eight patients who died, metastatic disease was the cause of death. In all 19 patients, the mean survival time from treatment of metastatic disease to death was 52.1 $\pm$ 37 months (range, 7–131 months; median, 38 months) and the 5-year survival rate was 54.5% (6 of 11 evaluable patients). Two of these 19 patients who underwent prolonged AV treatment before radiological signs of metastases exhibited high IRLs for the marker panel. In three patients, AV therapy was started soon after surgical removal of metastases (contra-lateral axillary lymph nodes [one] or liver [two]). In five patients, the survival time was 45, 60, 60, 90, and 115 months while the mean survival was 74 $\pm$ 28 months (range, 45–115 months; median, 60 months).

**Table 5** IRL: DFI, sensitivity (S), and LT of CEA, TPA, and CA 15-3 in the early detection of breast cancer distant metastases

Patients at the relapse	DFI (months)	CEA		TPA		CA 15-3	
		S%	LT (months, mean $\pm$ sd)	S%	LT (months, mean $\pm$ sd)	S%	LT (months, mean $\pm$ sd)
With AV therapy Patients (n)=10 Relapses (n)=11 <sup>a</sup>	36.2 $\pm$ 21	27.3	28.7 $\pm$ 27*	27.3	2.7 $\pm$ 2.1	36.4	15.5 $\pm$ 11.1
Without AV therapy Patients (n)=10 Relapses (n)=10	162 $\pm$ 79	50	7 $\pm$ 6.4	50	8.8 $\pm$ 8.5	40	8.5 $\pm$ 8.2
With and without AV therapy Patients (n)=19 <sup>a</sup> Relapses (n)=21	102 $\pm$ 87	38.1	15.1 $\pm$ 18.9	38.1	6.5 $\pm$ 7.2	38.1	12 $\pm$ 9.8

**Notes:** <sup>a</sup>Two of the 19 patients relapsed twice; in 1 of them both relapses occurred when the patient was under AV therapy, while in the other, the former relapse occurred when the patient was not, and the latter when she was under AV treatment; S% and LT refer to relapses; in both patients who relapsed twice DFI has been calculated from primary surgery to first relapse; \* $P=0.027$ .

**Abbreviations:** AV, adjuvant; DFI, disease-free interval; IRL, individual reference limit; LT, lead time.

**Table 6** IRL: sensitivity (S) and LT of CEA-CA 15-3 and CEA-TPA-CA 15-3 associations in the early detection of breast cancer distant metastases

Patients at the relapse	CEA-CA 15-3		CEA-TPA-CA 15-3	
	S%	LT (months, mean $\pm$ sd)	S%	LT (months, mean $\pm$ sd)
With AV therapy Patients (n)=10 Relapses (n)=11 <sup>a</sup>	63.6	21.1 $\pm$ 18.8*	90.9	15.6 $\pm$ 17.8
Without AV therapy Patients (n)=10 Relapses (n)=10	80	7.2 $\pm$ 7.1	100	7.9 $\pm$ 7.1
With and without AV therapy Patients (n)=19 <sup>a</sup> Relapses (n)=21	71.4	13.7 $\pm$ 15.1	95.2	11.7 $\pm$ 13.8

**Notes:** <sup>a</sup>Two of the 19 patients relapsed twice; in 1 of them both relapses occurred when the patient was under AV therapy, while in the other, the former relapse occurred when the patient was not, and the latter when she was under AV treatment; S% and LT refer to relapses; \* $P=0.041$ .

**Abbreviations:** AV, adjuvant; IRL, individual reference limit; LT, lead time.

## Description of two cases of early treatment with long-term survival and without clinical symptoms related to the relapse

Patient 1 was diagnosed with T1N1M0 in March 2012. Following primary surgery (quadrantectomy), she received six cycles of cyclophosphamide, methotrexate, 5-fluorouracil CH, followed by 7 years of hormone therapy (tamoxifen for 5 years plus vorozole for 2 years). At the time of the CEA CC, she had stopped AV treatment for about 3 years and was asymptomatic. The complete workup failed to detect metastasis. With her consent, she again began to take tamoxifen while a concomitant intense radiological monitoring was performed. During the 7 months of adjuvant tamoxifen, a progressive decrease in CEA values to normal range occurred. No radiological evidence of relapse occurred during this time. Subsequently, the patients stopped taking tamoxifen but continued with regular measurement of the marker panel and instrumental examinations. At the end of March 2013, although asymptomatic, an increase in CA 15-3 suggested a pending relapse. About 4 months after the CA 15-3 warning signal, whole-body positron-emission tomography (8-5-13) and whole-body CT (9-4-13) confirmed a secondary bone involvement at L4 and the patient was given tamoxifen.

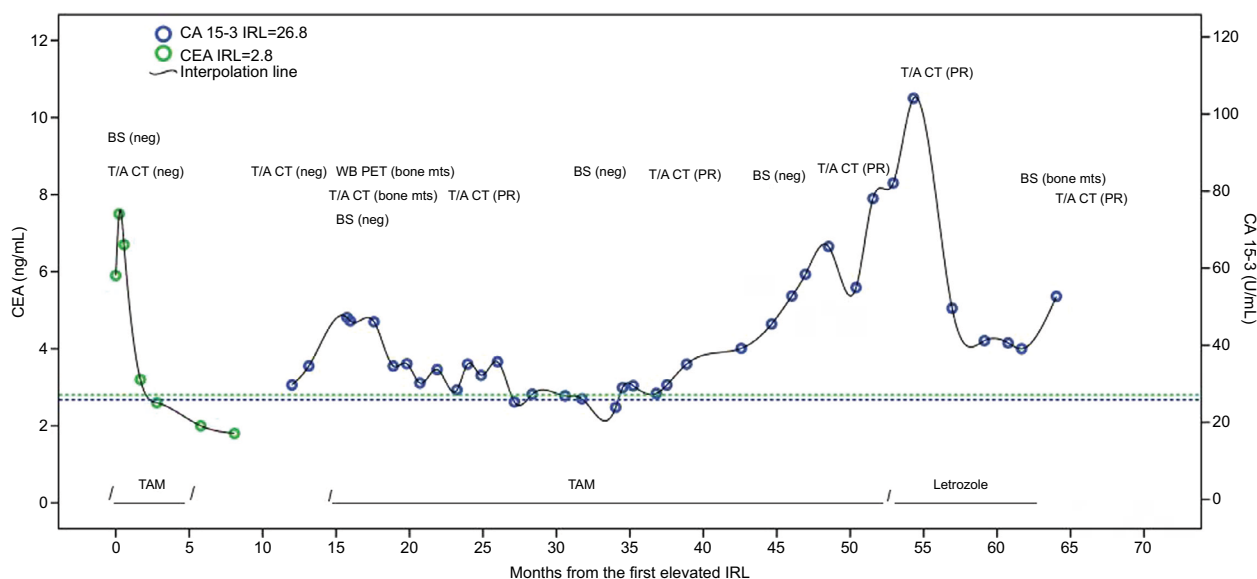
Following tamoxifen administration, CA 15-3 levels initially decreased to lower than the CA 15-3 IRL with a partial response at thoracic/abdominal CT. Thereafter, levels fluctuated for about 1 year and then increased up to October 2016 when tamoxifen was replaced with letrozole. Following

letrozole administration, CA 15-3 values again decreased although they stayed higher than the CA 15-3 IRL. During the interval from August 2013 to October 2017, the patient was asymptomatic and radiological monitoring was consistent with the partial response (Figure 1).

The second patient, who had T1N0M0 postoperative staging, underwent primary surgery (radical mastectomy modified according to Scanlon's technique) on February 1991 when she was 48 years. She received AV tamoxifen for 4 years. In January 2013, concomitant TPA and CA 15-3 CC were the warning signal of a pending relapse. At this time, she was asymptomatic and not receiving any systemic treatment. A complete workup however, failed to identify metastatic disease. As with the previous patient, these patients following consent began taking tamoxifen, ie, from April 2013 until November 2014. After commencing tamoxifen, TPA and CA 15-3 levels first progressively decreased and then fluctuated with levels marginally higher than the IRL. In November 2014, a further workup with whole-body CT showed diffuse bone metastasis. At that time, tamoxifen was replaced with letrozole, which led to levels of TPA and CA 15-3 lower than the IRL for these markers. During April 2013 to October 2017, the patient was asymptomatic. In addition, radiological monitoring from November 2014 to October 2017 documented stable disease (Figure 2).

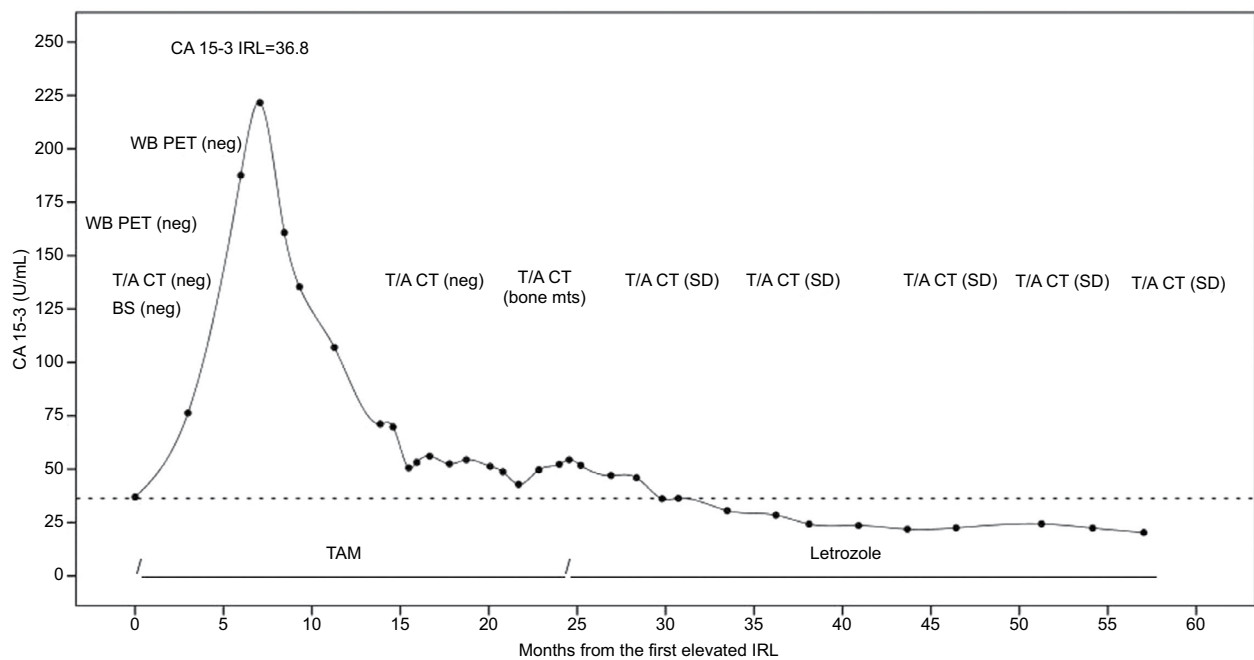
## Discussion

One of the main arguments against the routine use of markers in the postoperative management of asymptomatic women following a diagnosis of breast cancer is the limited efficiency



**Figure 1** Serum CEA and CA 15-3 behavior during postoperative follow-up of patient 1.

**Abbreviations:** BS, bone scintigraphy; CT, computed tomography; IRL, individual reference limit; mts, metastases; neg, negative; PET: positron emission tomography; PR, partial response; SD, stable disease; T/A, thoracic/abdominal; TAM, tamoxifen; WB, whole body.



**Figure 2** Serum CA 15-3 behavior during postoperative follow-up of patient 2.

**Abbreviations:** BS, bone scintigraphy; CT, computed tomography; IRL, individual reference limit; mts, metastases; neg, negative; PET: positron emission tomography; SD, stable disease; T/A, thoracic/abdominal; TAM, tamoxifen; WB, whole body.

of single markers for detecting early recurrences.<sup>2</sup> Although single markers have limited accuracy in detecting recurrences,<sup>2</sup> we show here that the combined measurement of CA 15-3, CEA, and TPA and the use of an IRL for defining a CC in marker levels predicted patient outcome with a sensitivity of 95.2%, specificity of 97.8%, and overall accuracy of 97.9%. Furthermore, combined measurement of the three markers provided an LT of ~1 year. A limitation of our study, however, is that only 19 (8.3%) of the 231 studied patients had evidence of distant metastases.

The key question however, is whether the early detection of recurrences followed by the early administration of systemic therapy has clinical utility. Despite the availability of the markers used in the investigation for over 20 years, it is unsatisfactory that we still lack evidence as to whether their measurement in asymptomatic women following a diagnosis of breast cancer is clinically useful. Clearly, this question needs to be urgently addressed in a prospective randomized trial. Should such a trial be carried out, the three markers with their IRLs described in this investigation might be considered for use in the test arm of the study.

Before concluding, we should state that two randomized prospective trials carried out in the 1980s and early 1990s<sup>20,21</sup> compared an intensive follow-up regime with a minimalist strategy for the postoperative surveillance of breast cancer patients. Both these trials indicated that physical examinations and mammography carried out timely did not significantly affect overall survival (OS) obtained using imaging

and routine laboratory examinations. However, the relevance of these old studies to the modern management of breast cancer patients is questionable because the determination of any of the abovementioned markers was not included.<sup>1</sup> Furthermore, as to early recurrence detection, the older instruments were less accurate than the modern ones. Perhaps, the most significant clinical change since these studies were performed is the increased number of new drugs tailored for subgroups of patients with recurrent breast cancers, particularly ER+ and HER2+ cancers.<sup>22-26</sup> Clearly, these deficiencies need to be addressed with a trial incorporating the measurement of serum markers and administration of modern treatments.

## Conclusion

We have shown that the combined measurement of serial levels of CA 15-3, CEA, and TPA predicts patient outcome following curative surgery for breast cancer with high accuracy and provides an LT of ~1 year for the detection of emerging metastasis. Therefore, a prospective randomized multicenter clinical trial comparing patients recruited to an intensive postoperative follow-up with CEA-TPA-CA 15-3 tumor marker panel as described here vs no follow-up should be carried out. This is to evaluate 1) whether a significant favorable impact on median survival from diagnosis of metastases and OS occurs in the intensive CEA-TPA-CA 15-3 follow-up arm vs no follow-up and 2) whether within the intensive CEA-TPA-CA 15-3 follow-up arm in ER+ patients, a hormone salvage treatment started

following the CC before radiological documentation significantly prolonged the just mentioned end points compared to patients starting hormone salvage therapy after metastases have been radiologically documented.

## Ethics and consent statement

The research and consent process were approved by the Council of the Department of Internal Medicine at Pisa University. All the studied patients gave verbal informed consent, witnessed in the presence of a family member, and were free to remove themselves from the trial at any time.

## Disclosure

The authors report no conflicts of interest in this work.

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