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Eur J Cancer, Vol. 27, No. 11, pp. 1440–1444, 1991.
Printed in Great Britain

0277-5379/91 $3.00 + 0.00

Serial Serum MCA Measurements in the Follow-up of Breast Cancer Patients

Ofer Merimsky, Moshe Inbar, Mara Hareuveni, Bruria Witenberg, Yoram Wolman and Samario Chaitchik

Mucin-like carcinoma-associated antigen (MCA) was serially assayed in 58 women with histologically proven breast cancer after their treatment for primary disease. MCA sensitivity and specificity were 87.5% and 76.9%, respectively, and the positive predictive value 82.4%. 10 patients had elevated MCA and no evidence of disease (NED) during their follow-up, of whom 4 finally developed overt metastases. The 4 had a mean (S.D.) MCA value of 46.48 (18.26) U/ml during the lead time, versus 18.76 (2.69) U/ml in the other 6, who are still at high risk for developing overt metastases. Raised levels of MCA in patients with NED create a dilemma of "treat" versus "wait and see". Early treatment of patients with serially uprising MCA levels should be evaluated in a prospective randomised study to assess its ability to prevent or delay the development of overt metastatic disease and influence survival.
Eur J Cancer, Vol. 27, No. 11, pp. 1440–1444, 1991.

INTRODUCTION

THE USE of tumour markers for the diagnosis, assessment and follow-up of breast cancer patients has until recently been disappointing. In order to predict early clinical recurrence, a reliable marker of high sensitivity and specificity, which could detect small tumour burdens, is required. The widely used carcinoembryonic antigen (CEA) has been proven to be of little value for predicting clinical recurrence and has successfully monitored only 60% of patients with metastatic disease during treatment, as the others did not show elevated serum CEA [1].

Mucin-like carcinoma-associated antigen (MCA) is a high molecular weight glycoprotein, produced by oestrogen-dependent and oestrogen-independent mammary carcinoma cells. It is also produced (to a much lesser extent) by several other normal tissues such as breast ducts and renal distal tubules [2]. MCA levels are not elevated in over 95% of patients with localised

Table 1. Oestrogen (ER) and progesterone (PR) receptor status.

	ER+	ER−	ER?
PR+	10	3	0
PR−	12	16	0
PR?	0	1	16

No. of patients.
(+) = Positive, (−) = negative, (?) = unknown.

breast carcinoma, and in 79% of patients with locoregional disease. Hence, MCA cannot be used for screening of breast cancer [3, 4]. MCA is not elevated in smokers (in contrast to CEA) nor in cases of benign breast tumours, such as papillomas and fibrocystic disease [5, 6].

MCA measurements in normal healthy volunteers range between 0–17 U/ml, with an average of 7 U/ml. Serum levels over 11 U/ml were found in only 5% of healthy individuals, and levels of 17 U/ml in only 1%. Benign disorders giving rise to elevated MCA levels include liver diseases, such as hepatitis and cirrhosis (rarely exceeding 11 U/ml), pregnancy and breast disorders such as mammary dysplasia. Thus, MCA levels up to 11 U/ml are considered normal, whereas those over 14 U/ml are considered pathological. Values between 11 and 14 U/ml are suspect and need repeated MCA measurements [7]. The greater specificity and the higher positive predictive value of MCA compared with other markers renders it useful for diagnostic purposes in detecting early recurrence [5,8,9].

Our study was aimed at assessing the role of serial MCA measurements in the follow-up of patients with breast cancer and in the early detection of metastatic disease.

PATIENTS AND METHODS

58 Jewish, female, breast cancer patients, who were on follow-up at our institute of oncology from October 1988 to September 1990, had serial serum MCA determination. All the patients had histologically proven cancer of the breast and had completed definitive treatment. None had any other known malignancy. Follow-up included physical examination, chest X-rays, liver ultrasound, bone scan and measurement of serum CEA and MCA levels every 3–4 months.

The MCA level was evalued in the 58 patients in at least 3 consecutive assays over the follow-up period. In 9 patients MCA was assayed only late in the follow-up period because of its earlier unavailability. In all the patients MCA test was performed postoperatively, and in 13 also pre-operatively. The patients' ages ranged from 28–74 years with a median of 46.5 years. 30 patients were premenopausal and 28 were postmenopausal. At the time of diagnosis, 25 of the 58 patients had localised disease (node-negative), 31 had axillary lymph node involvement, 2 had metastatic disease, 47 patients had infiltrating duct carcinoma, 6 had infiltrating lobular carcinoma, while 5 had mixed infiltrating duct and lobular carcinomas. The steroid receptor [oestrogen (ER) and progesterone (PR)] status of our patients is shown in Table 1. Treatment for primary tumour was mastectomy (either simple or modified radical, and axillary dissection) in 51 patients, lumpectomy and axillary lymph node sampling in 4, and biopsy only in 3 patients (1 with inoperable locoregional disease, and 2 with metastatic disease). Those with node-positive disease received adjuvant chemotherapy or hormonotherapy according to their age and receptor status: adjuvant chemotherapy was given in node-positive premenopausal women and in node-positive receptor-negative postmenopausal women under 65 years of age, and adjuvant tamoxifen in postmenopausal receptor-positive patients. No adjuvent treatment was given to node-negative patients.

Table 2. MCA level vs. clinical status in 58 patients

MCA (U/ml)	NED	Disease	Total
0–11	13	3	16
11–14	7	1	8
>14	6	28	34

NED = no evidence of disease.

Serum MCA determination was performed by two of us (BW, MH) using the enzyme immunoassay (EIA) kit for MCA (Hoffmann–La Roche, Switzerland). Blood samples were drawn from the patients and kept at 4°C for 4–6 h until separated. Sera were kept at −20°C until assayed for MCA. Each sample was assayed in duplicate, and a mean value was calculated. MCA levels were of ≥ 14 U/ml was considered patholgical, while lower MCA levels were considered normal. The lead time was calculated from the first documentation of an elevated MCA level to the diagnosis of overt metastatic disease.

RESULTS

MCA values and correlation with clinical status are presented in Table 2. Normal MCA levels were found in a group of 20 patients with no evidence of disease (NED), after treatment for the primary disease (with or without adjuvant treatment) and throughout the follow-up period. Values ranged from 2.59 U/ml to 13.53 U/ml [mean (S.D.) 9.32 (3.01) U/ml]. Normal MCA levels were also found in 4 out of 32 patients with evidence of disease: 2 had local recurrence (9.65 U/ml; 11.88 U/ml) and 2 metastatic disease (8.10 U/ml in a case with lymph node metastases and direct invasion of the brachial plexus; 6.00 U/ml in a patient with local recurrence and lung metastases).

34 patients had elevated MCA levels (> 14 U/ml), 28 of whom had clinically overt metastatic disease. The MCA values of those 28 patients ranged from 15.47 U/ml to 1170 U/ml [mean (S.D.) 129.87 (258.65) U/ml]. There was no lead time in this group, and the rise in MCA level occurred concomitantly with the appearance of metastases. There was no correlation between MCA levels and the distribution of metastases in these patients. Neither was there any correlation between MCA levels and the number of metastatic sites (Table 3). MCA levels were not

Table 3. MCA levels vs. number of metastatic sites

Metastatic sites	No. of patients	MCA levels (range) (U/ml)	Mean (S.D.) (U/ml)
1	8	34.1 –153.3	67.15 (39.9)
2	10	16.45–173.7	44.37 (47.0)
≥3	10	15.47–1170	265.53 (406.43)

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Revised 15 May 1991; accepted 18 July 1991.

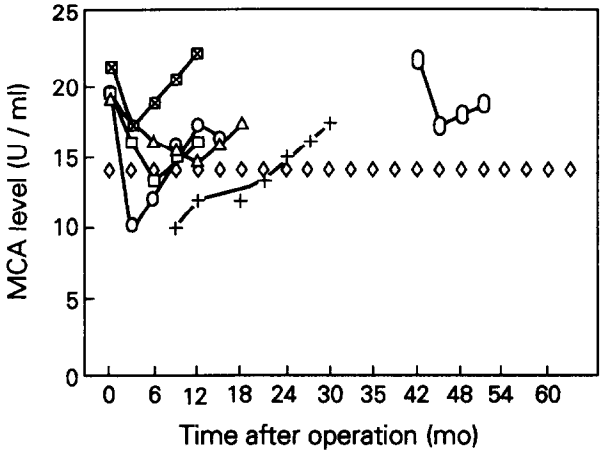

Fig. 1. MCA kinetics in patients 1–6 before operation, and during follow-up, while disease-free. The first down-slope in graphs 2–5 is attributed to the effect of surgery on tumour load, and in graph 6 to variation in MCA level. ◇ = Cut off level, + = patient 1, 0 = 2, □ = 3, △ = 4, □ = 5, 0 = 6.

significantly higher even in patients with 3 or more sites of metastases.

5 of the 28 patients had only bone metastases, and their higher values of MCA were 31.2, 34.1, 37.5, 54.9 and 74.7 U/ml [46.48 (18.26) U/ml]. 12 patients had bone and at least one more site of metastatic disease. Their higher values of MCA levels ranged from 16.45 to 667 U/ml [143.68 (235.03) U/ml]. The others had various combinations of metastatic sites.

4 patients of the 28 with metastatic disease started their surveillance with NED, but since then overt metastases have already developed. In this group, MCA was not available in the immediate postoperative period, hence MCA measurements were performed only much later during their follow-up. MCA levels were elevated in their clinically disease-free period, and ranged from 23.0 to 153.3 U/ml [70.63 (58.32)] and preceded overt metastatic disease by 3, 6, 16 and 21 months (Figs 1, 2). The other 6 patients out of the 34 with pathological MCA levels still remain disease-free. They started their MCA monitoring before the operation, hence the first decline in the marker level (Figs 1–2). The subsequent rise reflects, in our opinion, early

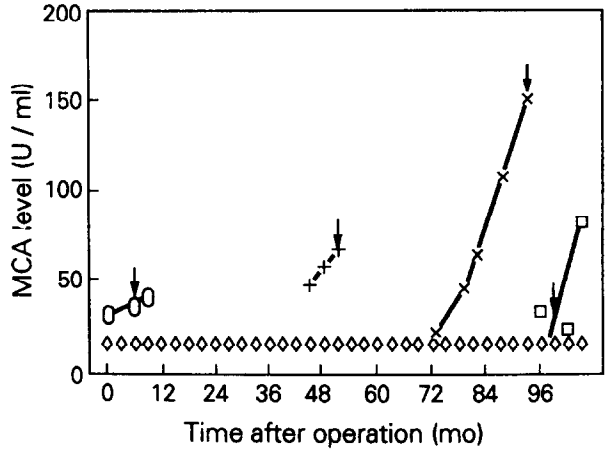

Fig. 2. MCA kinetics in patients 7–10 during the follow-up period, while having elevated MCA levels and no evidence of disease. Arrows indicate the point of metastatic surge in each case. ◇ = Cut-off level, □ = patient 7, + = patient 8, 0 = patient 9, × = patient 10.

Table 4. Clinical data of patients with NED and elevated MCA level

Patient no./age	Menopausal status	Stage†	ER/PR status	MCA level (U/ml)*	Lead time (mo)	Outcome
1/52	Pre	T_1N_0	0/0	17.4	> 5	NED
2/49	Pre	T_1N_1	0/0	17.3	>13	NED
3/74	Post	T_1N_0	0/0	22.4	>21	NED
4/44	Pre	T_2N_0	0/0	17.5	>11	NED
5/64	Post	T_2N_1	66/0	16.0	>11	NED
6/73	Post	T_2N_1	0/0	21.9	>14	NED
7/46	Post	T_1N_0	25/0	23.0	3	Abdominal spread
8/47	Pre	T_1N_1	0/31	68.7	6	Pleural effusion
9/61	Post	T_4N_1	28/0	37.5	8	Bone metastases
10/45	Pre	T_3N_1	31/0	153.3	21	Abdominal spread

* At the end of the lead period.
† TNM (M = 0).

evidence for disease recurrence; they were considered as the false positive cases. In this group MCA ranged from a higher value of 16.01 U/ml to 22.37 U/ml [18.76 (2.69) U/ml].

The common bad prognostic factor for 90% of the 10 patients with NED and elevated MCA levels was a negative PR. 1 patient had positive PR but negative ER. Clinical data of these 10 patients, including the lead time and outcome, are detailed in Table 4.

Negative lead time (overt metastatic disease preceded the rise in MCA level) of 6–21 months was observed in 3 out of the 28 patients with metastatic disease at various sites, including bone, lung, liver and brain. Successive MCA measurements showed high levels, so these 3 "false negative" patients were virtually MCA-secretors. This secretion was probably tumour burden-dependent, hence small tumour mass secreted MCA up to a "normal" level. These 3 cases were finally considered as true positive (for needs of sensitivity and specificity calculation) due to their higher MCA level.

The sensitivity of MCA in our series was 87.5%, and the specificity 76.9%. The positive predictive value was 82.4%, and the negative predictive value 83.3%.

Symptomatic disease was presented by the patients themselves in 29 out of the 32 patients with evidence of disease and an elevated MCA level. Among the other 3 patients, 1 had NED for 21 months, when an asymptomatic abdominal mass was found. The other 2 were asymptomatic in spite of a positive bone scan, for 2 and 3.5 months before the appearance of bone pains. The 4 patients with normal MCA level in spite of clinically overt metastatic disease, were all symptomatic.

Of the 10 patients with NED and elevated MCA level, 3 developed a symptomatic overt disease, and 1 (mentioned above) had an asymptomatic abdominal mass. The other 6 patients are still disease-free, symptom-free but MCA-positive.

DISCUSSION

Our series included only those patients who had at least 3 consecutive serum MCA determinations. By this, we considered only the patients who had a clear trend in their marker kinetics, hence minimising the false positive cases and increasing the likelihood of having sensitivity, specificity and positive predictive value, closer to their "real" values.

However, the use of markers is limited by the inability of

several metastases to express or secrete these proteins in amounts sufficient for detection above the cut-off level.

The sensitivity and the specificity of MCA as a marker for breast cancer were calculated according to the correlation between the level of MCA, and the clinical status of the patients at a certain time. In our series, we found a sensitivity of 87.5% and a specificity of 76.9%—very similar to the data reported by Roche (MCA kit leaflet). The false positive results of MCA as a test for presence of breast cancer metastases may be only temporary, because overt metastases may develop later. False negative results may also be temporary, and turn into true positive, dependent on an increase in tumour load or formation of new MCA-secreting clones.

MCA was found to have a high positive predictive value in our series, as also reported by others [5, 8, 9]; as well as a high negative predictive value [10]. In 97% of cases with a negative bone scan and MCA levels below 11 U/ml, distant metastases could be histologically excluded [10].

The use of MCA (or other markers) creates a dilemma of "to treat" or "not to treat". In the presence of normal MCA levels and NED we all agree that further follow-up is indicated. In the case of either normal or elevated MCA levels and symptomatic metastatic disease, patients are treated. However, when there is NED and the MCA level is elevated and highly suggestive of metastatic disease, what should the policy be?

The following case report serves an example for the dilemma. A 45-year-old nurse (Table 4, patient 10), underwent a modified radical mastectomy for a $T_3N_1M_0$ infiltrating lobular carcinoma (ER = 31, PR = 0 fmol/l), received 6 courses of adjuvant CMF (cyclophosphamide, methotrexate, 5-fluorouracil), and was irradiated to the chest wall. For 5.5 years she was disease-free. CEA then started to rise (MCA was not yet available). During the next 21 months follow-up, she paid 31 visits to the oncology outpatient clinic, had 5 consultations to other clinics, 5 chest X-rays, 3 bone scans, 2 mammographs, 3 abdominal ultrasonographs, 6 computed tomography (CT) studies of the chest, abdomen, pelvis and brain, 2 magnetic resonance imaging (MRI) studies of the pelvis, 1 bronchoscopy because of suspicious changes on chest plain film, 1 Pap smear, 1 colposcopy, 1 gastroscopy, 1 colonoscopy, 1 thyroid scan because of palpable nodule, 6 complete blood counts, 13 CEA measurements, 5 MCA determinations, and 4 biopsies: breast, colon, cervix and bone marrow. The results were all negative for malignancy. Therapeutic trials with tamoxifen, medroxyprogesterone-acetate and luteinising hormone-releasing hormone (LHRH) agonist (decapeptyl) resulted in progressive elevation of the MCA and CEA (Fig. 3). Finally, an abdominal mass detected radiologically was confirmed histologically to be a metastatic lesion of breast cancer.

There are four options for resolving the MCA dilemma. The first is to continue follow-up until there is clear indiction for treatment, such as pain or respiratory distress. This option might shorten the "psychological" disease-free interval, causing a great psychological burden for the patient: her anxiety is severe and she feels that time is being wasted. It is possible in some cases not to inform the patient of the abnormal results of a test of still unproven veracity, and of the "four in five chance" of having an incurable disease. This approach will prevent anxiety reactions, but will not resolve the dilemma.

The second option is to re-evaluate the patient every 3–4 months by extensive radiological studies and blood analyses (including tumour markers). This option is rather expensive, and the results might be inconclusive. Will we proceed by performing random biopsies or even an explorative laparotomy? This option might also be psychologically harmful.

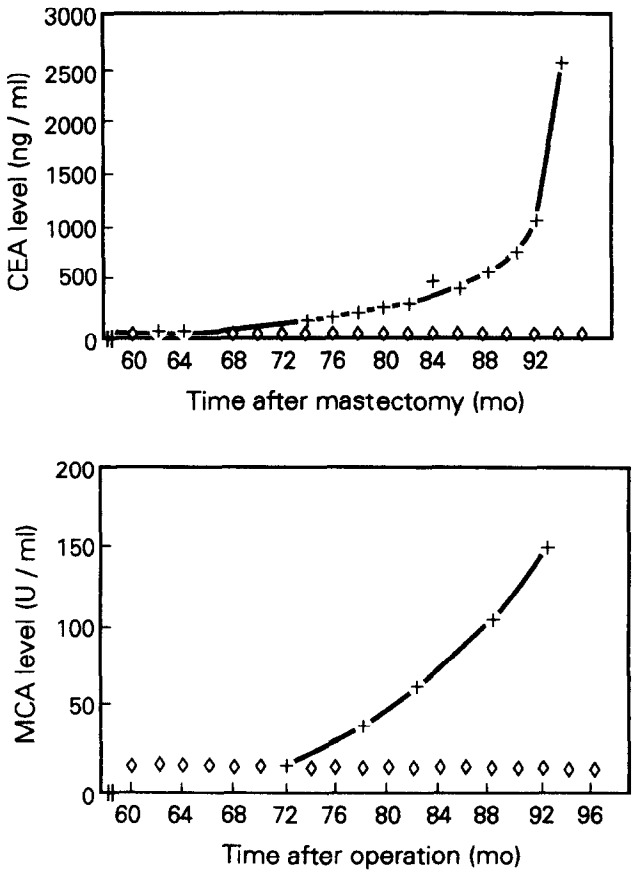

Fig. 3. (a) CEA and (b) MCA kinetics in patient no. 10 during her clinically disease-free period. ◇ = Cut-off level, + = patient.

The third option is to treat and monitor the patient by the same marker. This marker secretion may be due to tumour cell clones too small for clinical or radiological detection, but which may be silently disseminating to various organs [8]. Treatment of an asymptomatic breast cancer patient with metastatic disease is controversial, because it is never been shown that the treatment of asymptomatic but detectable metastatic breast cancer offers any survival benefit over symptomatic metastatic disease [11, 12]. Recent data from the NSABP indicate that routinely scheduled bone scans to detect metastases in asymptomatic breast cancer patients are relatively unrewarding: there is no evidence that the treatment of patients with asymptomatic skeletal metastases improves survival over that obtained when one waits for the appearance of symptoms [13]. This statement, in our opinion, is based on the fact that a relatively big tumour load is needed to be detected by ancillary imaging techniques. Such a tumour load is already beyond curative treatment. The use of MCA may enable us to detect a much smaller tumour load (provided it secretes MCA), that may be treated earlier, resulting in some survival gain.

However, considering the positive predictive value of 82.4% in our series, 17.6% of the patients (with NED and elevated MCA) might be treated unnecessarily. Furthermore, some treatment may be started while the patient is completely asymptomatic, resulting in a situation where palliative treatment possibilities, when needed, are reduced because of the former treatments. On the other hand, if previous treatment failed when the tumour

load was much smaller, no response is expected when overt disease is being treated.

The fourth option is not to measure MCA routinely in the follow-up of breast cancer patients. It has been stated that bone scan and other imaging procedures, as well as CEA, do not uniformly detect occult metastases and do not detect curable disease. They are useful in the evaluation of symptomatic patients, but their value in routine follow-up is uncertain [14]. This option should be considered only if the role of MCA in early detection of recurrent disease has already been assessed.

Avoiding new methods for follow-up and early detection of metastatic disease will surely prevent any further progress in the field of tumour markers. More than that, if metastatic disease of the breast is still curable at the time of the first uprise of this relatively sensitive marker, long before the tumour load enlarges and the disease becomes clinically overt, we might never overcome this malignancy, due to underestimation of MCA. For the time being, this is only a speculation, which should be further evaluated in prospective randomised studies.

Proceeding on our results, we examined the MCA as a predictor for development of metastatic disease in the 10 patients with NED (Table 4). It has already been stated in the literature that MCA was found to be a reliable marker for early detection of recurrent disease, and a continuous increase in MCA concentrations may precede clinical diagnosis of metastases by several months [8]. 3 of the 4 who developed metastatic disease had malignant effusion and 1 bone involvement. The 4 had a wide range of MCA levels [mean (S.D.) 70.63 (58.32) U/ml] at the time of metastatic surge, after being disease-free during the lead time. 6 patients still have elevated MCA levels [18.65 (2.69) U/ml] with NED, 5 of whom are at risk for development of overt metastases—at least according to the positive predictive value found in our series. The mean MCA level of the 4 patients with overt metastatic disease is significantly higher than that of the 6 disease-free patients.

In our series the uprising MCA preceded the appearance of symptoms and overt disease in 4 of the 10 patients with NED. The other 6 are still symptom-free and disease-free. Literature data suggest that most recurrences after mastectomy are symptomatic, but in approximately one third of patients, asymptomatic recurrence are detected on routine follow-up physical examination [15].

It is true that in the majority of patients MCA levels are only elevated in clinical overt recurrent disease, and raised MCA levels are not helpful in the early detection of recurrent subclinical disease in 80–85% of cases. However, if 15–20% of the patients (the 10 patients with NED and elevated MCA, out of 58 patients in the series) will do have any benefit from MCA measurement by induction of early treatment. This test may be found to be worth performing.

Should elevated MCA level be an indication for early treatment in patients with NED? The answer is obscure. To be practical, if one does not consider an elevated MCA level to be a possible indication for treatment, there is no need to measure MCA during the follow-up of patients with NED. On the other hand, because of the presently rather high false positive rate, it is impossible to rely only on elevated MCA levels for the diagnosis of recurrent disease. Systemic treatment of breast cancer metastases only on the basis of elevated MCA levels without any known metastatic site, may be therefore not justifiable at the present time. Further prospective studies are needed to evaluate the positive predictive value of elevated MCA level in NED state, especially the use of relatively non-toxic treatments such as tamoxifen.

In summary, MCA is not an ideal marker due to rather low sensitivity and specificity, but is one of the best presently available for breast cancer follow-up. MCA may be used as a detector of subclinical development of metastatic disease, but should be further evaluated in larger groups of patients with NED. Its role as an indication for early treatment of imminent overt metastatic disease has not yet been fully defined and may be evaluated in prospective randomised studies. MCA should be assessed as a monitor for treatment of metastatic disease in order to detect early failures. In future, MCA should be measured at a pre-operative set-up, and failure to return to normal level following surgery and/or radiotherpay to the primary disease, especially in node-negative patients, should be evaluated as an indication for adjuvant systemic treatment.

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