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Ca 15-3 in the follow-up of localised breast cancer: a prospective study

R. Kokko[a,*], K. Holli[b], M. Hakama[c]

[a]*Department of Oncology and Central Hospital of Central Finland, Jyväskylä and University of Tampere, Tampere, Finland*
[b]*Department of Palliative Medicine, Tampere University Hospital and University of Tampere, Tampere, Finland*
[c]*University of Tampere School of Public Health, Tampere, Finland*

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Abstract

Altogether, 243 female breast cancer patients with localised disease diagnosed between 1991 and 1995 in the Tampere University Hospital area were followed prospectively after primary treatment until the first relapse. In the follow-up period, the serum tumour marker Ca 15-3 was analysed every 6 months to ascertain the validity of this marker in detecting the first relapse. The sensitivity and specificity of the test were analysed in different metastatic situations. During the 5 years of follow-up, 59 (24%) relapses were discovered. Ca 15-3 was elevated in 21/59 (36%) of the relapsed cases at least once. The 59 patients were subjected to 199 tests, of which 25 (13%) were positive. Among the 184 patients without recurrence, there were 6 (3%) with a positive Ca 15-3 level. The test failed to detect locoregional relapse or contralateral breast cancer. It was elevated in approximately half of bone-only metastases and in all of the liver-only metastases. In the pulmonary-only recurrences, the marker value was not elevated. We conclude that the Ca 15-3 tumour marker test is specific, but not sensitive enough to indicate the first relapse earlier than other methods. The positive predictive value especially remained poor in patients with a relatively good prognosis. Our results confirm that the test is not suitable alone for breast cancer follow-up.

Keywords: Breast cancer; Follow-up; Tumour marker Ca 15-3; Sensitivity; Specificity; First relapse

1. Introduction

The serum tumour marker Ca 15-3 is a glycoprotein secreted by breast cancer cells. It can be measured in sera radioimmunologically with the monoclonal antibodies DF3 and 115-D8. In clinical practice, Ca 15-3 is frequently used in the routine follow-up of breast cancer patients, as well as in estimating the response to therapy in a metastatic setting.

There are few studies estimating the value of the tumour marker Ca 15-3 in prospective trials. In our prospective study, the Ca 15-3 test was applied routinely and analysed twice a year in the follow-up of breast cancer patients after primary treatment. The purpose of our study was to establish, whether the use of this marker test could offer clinical benefit for patients through the earlier diagnosis of recurrent disease. We were interested in the specificity and sensitivity of the test in indicating the first relapse. Both patient- and test-specific sensitivity and specificity were evaluated. We investigated whether the specificity and the sensitivity of the tumour marker were dependent on the metastatic site. The predictive values were also calculated.

2. Patients and methods

Altogether 243 consecutive female patients with localised breast cancer diagnosed in the area of the University Hospital of Tampere from May 1991 to December 1995 and followed-up at the Department of Oncology were included in this prospective follow-up study after primary treatment for breast cancer. The study was approved by the Tampere University Hospital Ethical Committee and oral informed consent of patients was obtained.

Patients were followed-up for 5 years or until the first either local or distant relapse, whichever occurred first. Chest X-ray was taken routinely every 6 months and

* Corresponding author at: Central Hospital of Central Finland, Department of Oncology, Keskussairaalantie 19, 40620 Jyväskylä, Finland. Tel.: +358-14-691-811; fax: +358-14-691-279.
E-mail address: riitta.kokko@ksshp.fi (R. Kokko).

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mammography every year, abdominal ultrasound and bone scintigraphy routinely every second year or when recurrent disease was suspected. Clinical examination was undertaken regularly every 6 months together with routine laboratory blood tests (erythrocyte sedimentation rate, haemoglobin, leucocyte and platelet counts, liver enzymes, alkaline phosphatase and transaminase and serum electrolyte sodium and potassium) were taken regularly twice a year.

Standardised Ca 15-3 measurements were taken routinely every 6 months. Tumour marker analysis was made from sera by immunoradiometry with two monoclonal antibodies using ELSA Ca 15-3 reagents from the Cis Bio International ORIS Group, Gif-sur-Yvette, France, and the apparatus was the 1277 Gammamaster, Wallac, Turku, Finland. This method was introduced into routine use in July 1993, but was used in Tampere University Hospital area during the whole study period from 1991 to 1995. Test values $\geqslant 40$ IU/l were considered elevated (positive).

The validity of Ca 15-3 in the follow-up was estimated in relation to both the patients and the tests. We defined patient sensitivity as the number of relapsed patients with positive tumour markers among all of the relapsed patients. Patient specificity was estimated as the number of patients with Ca 15-3 in the normal range among those without relapses. As there were several tests per patient, we also defined test validity and estimated it as follows: test sensitivity was estimated as the number of positive tests among all tests in patients with relapse, test specificity as the number of tests within the normal range among all tests in patients without relapses. Test sensitivity was, furthermore, estimated restricting the positivity of the Ca 15-3 test only to the 12 months preceding the recurrence.

The diagnostic significance of Ca 15-3 was estimated in terms of positive and negative predictive values. These are indicators relevant to the patients (and the doctor), but are not characteristics of the test only. Hence, only patients as units of observation were used in the estimation of predictive values. Positive predictive value was defined as the proportion of patients with recurrence among patients with a positive Ca 15-3 and negative predictive value as the proportion of patients without recurrence among all patients with Ca 15-3 within the normal range.

The median age of the 243 patients was 58.2 years (range, 32–91 years); 9% were younger than 45 years of age and 10% were older than 75 years of age. Approximately one-third (29%) of the patients were pre-menopausal and two-thirds (71%) post-menopausal. Tumour size was classified as T1 class in 64% of cases and as T1 + T2 classes in 97% of cases. The proportion of node-negative cases was 75%. Oestrogen receptors were positive in 65% and progesterone receptors in 53% of cases. Mastectomy and conservative operation were equally common (50 and 48%, respectively). Most of the patients (70%) received postoperative radiation therapy (total radiation dose 50 Grey). Adjuvant systemic therapies were rarely used: only 13% of patients received hormonal therapy and 15% chemotherapy (Table 1).

Table 1
Characteristics of the patients and their disease ($n = 243$)

Characteristics	*n* (%)
Age (years)	
$\leqslant 44$	22 (9)
45–54	81 (33)
55–64	61 (25)
65–74	55 (23)
$\geqslant 75$	24 (10)
Menopausal status	
Pre	70 (29)
Post	173 (71)
Tumour size	
T1	156 (64)
T2	79 (33)
T3-T4	7 (3)
Unknown	1 (0.5)
Axillary nodal status	
N−	181 (75)
N+	59 (24)
Unknown	3 (1)
Histology	
Ductal invasive	179 (74)
Lobular invasive	28 (12)
DCIS	15 (6)
Others	18 (7)
Unknown	3 (1)
Hormone receptor status	
ER−	54 (22)
ER+	158 (65)
ER unknown	31 (13)
PR−	84 (35)
PR+	130 (53)
PR unknown	29 (12)
Surgery	
Conservative	116 (48)
Mastectomy	122 (50)
No operation	4 (2)
Unknown	1 (0.5)
Radiation therapy	
No	73 (30)
Yes	170 (70)
Adjuvant endocrine therapy	
No	211 (87)
Yes	32 (13)
Adjuvant chemotherapy	
No	206 (85)
Yes	37 (15)
Total	243 (100)

DCIS, ductal carcinoma in situ; ER, Oestrogen Receptor; PR, Progesterone Receptor.

Table 2
Numbers and percentiles of elevated tumour marker Ca 15-3 in relapsed patients and in test samples ($n=1294$) in the study population ($n=243$)

Ca 15–3 elevated[a]	Recurrence					
	Yes		No		Total	
	Patients *n* (%)	Tests *n* (%)	Patients *n* (%)	Tests *n* (%)	Patients *n* (%)	Tests *n* (%)
Never	38 (64)	174 (87)	178 (97)	1084 (99)	216 (89)	1258 (97)
Ever[b]	21 (36)	25 (13)	6 (3)	11 (1)	27 (11)	36 (3)
Total	59 (100)	199 (100)	184 (100)	1095 (100)	243 (100)	1294 (100)

[a] Ca 15-3 $\geqslant$ 40 IU/l.
[b] Only 1 patient had Ca 15-3 elevated more than 12 months before recurrence.

3. Results

During the 5 years of follow-up 59 (24%) recurrent diseases were discovered (Table 2). Altogether 1294 marker test samples from these 243 patients were taken, a median of 5.3 tests per patient. Altogether 199 marker test samples were taken from the 59 patients with recurrent disease, a median of 3.4 tests per patient. In the tumour marker-positive recurrences, the median Ca 15–3 value was 119 IU/l and the mean value 227 IU/l (range 40–760 IU/l).

The mean lead time (the time interval from the first positive tumour marker to the verification of recurrent disease) was 89 days (range 0–1091 days) and the median lead time was 18 days.

Approximately one-third of recurrences were detectable by the Ca 15-3 tumour marker levels—patient sensitivity was 36% (Table 2). When all of the tumour tests taken during the 5 years of follow-up period (1294) were taken into consideration, sensitivity was lower, 13% (test sensitivity). In the study population ($n=243$), there were 6 patients who had elevated marker and no recurrence (false-positive, 3%). The test was false-positive 11 times in these 6 patients. Hence, the patient specificity was 97% and the test specificity 99%.

Table 3
Different site recurrences ($n=59$) and Ca 15-3[a] in the study population ($n=243$)

Site of recurrence	Ca 15-3 elevated (*n*)	Patient sensitivity (%)	Total number of recurrences (*n*)
Any site	21	36	59
Liver-only	4	100	4
Bone-only	7	47	15
Multiple sites	7	54	13
Lymph nodes-only	1	20	5
Skin-only	1	7	14
Lung-only	0	0	5
Contralateral breast-only	0	0	3
Other site	1	100	1

[a] Ca 15–3 elevated, <40 IU/l.

The positive predictive value (probability with elevated Ca 15-3 to have breast cancer) was 78% and negative predictive value (probability with normal Ca 15-3 not to have breast cancer) was 82%. With elevated tumour marker, recurrent disease could be confirmed in approximately 4 out of 5 patients. When the test value was in the reference area, recurrent disease could likewise be ruled out in approximately 4 out of 5 patients.

Ca 15-3 was elevated in 21 recurrences out of 59—in all of the 4 patients with liver metastases (100%), in nearly half of those with bone-only metastases (47%), in approximately half of the multiple metastases cases (54%) and in none of the 5 lung-only metastases cases. The marker value was elevated in 20% of patients with lymph node-only recurrences and in only 1 patient with skin-only metastases (7%). Three contralateral breast cancers were diagnosed among this patient population and none of them had elevated Ca 15-3 marker. The first relapse was multiple in 13 cases, bone-only in 15, skin-only in 14 and liver-only in 4 (Table 3).

4. Discussion

The tumour marker Ca 15–3 has usually been studied at the primary diagnosis of breast cancer and in metastatic settings. It has been found elevated in breast cancer in stage I in 9%, stage II in 19%, stage III in 38% and stage IV (distant metastatic disease) in 75% [1]. Multiple metastatic disease and large tumour burden correlate with high marker values [2,3]. Metastatic disease in liver, bones and lung and metastatic pleural effusions have especially given rise to pathological Ca 15-3 values [4].

The published literature contains only a few prospective studies concerning the use of the Ca 15-3 marker in the follow-up of breast cancer that was local at diagnosis. The numbers of patients in previous studies have been too small to allow any firm conclusions [5–8].

The present study was prospective and the median follow-up time per patient was fairly long, 4.3 years. The number of patients was 243 and the follow-up

schedule was the same for every patient. We consider our study population to be reasonably representative.

The sensitivity and specificity, as well as the negative and positive values, obtained for the tumour marker Ca 15-3 are difficult to compare between different studies due to the many methodological differences (cut-off points, test assay methods), heterogeneous patient populations (nodal ±, low-risk/high-risk tumours, age distribution) and different follow-up times and schedules [3,5,9]. According to Gion and colleagues [10], the patient sensitivity of Ca 15-3 in the different studies ranged between 33 and 78% and the patient specificity between 60 and 93%. We studied both patient and test sensitivity and found that patient sensitivity (36%) and test sensitivity (13%) were different depending on whether the unit was the patient or the test.

In order to improve the sensitivity and specificity (clinical validity) of the Ca 15-3 marker a 26% elevation change in marker value levels occurring twice or a 66% elevation change occurring once above the cut-off value [8] is being considered as significant. Gion and colleagues [10] found the normal variation to be substantial, especially with low values. In our study, normal values were <40 IU/l and pathological were values $\geqslant 40$ IU/l; in the Ca 15-3 positive relapses, the mean tumour marker value was 227 IU/ml and the median tumour marker value was 119 IU/ml. Both values were considerably beyond the upper limit for the reference value of the test.

Ca 15-3 is not the most specific tumour marker: it is elevated in 5–6% of healthy people, especially in liver and biliary diseases and often in mastopathic disease of the breast [1,2,5,11]. It can also be unspecifically elevated in other cancer diseases (e.g. ovarian cancer). In this study, there were 11 false-positive tests among the 1095 tests carried out among the non-relapsing patients (11/1095, 1%). Among 184 patients without relapse, there were false-positive results in 6 patients (3%). The reasons for these few marginally elevated false-positive results in our study may be as a result of other diseases, benign conditions and intra-individual marker level variations. Söletormos found the intra-individual variation of Ca 15-3 tumour marker values to be approximately 7%.

In the present study during the follow-up period (median 4.3 years) recurrent disease was found in 24% of the patients. Every third relapse was detectable on the basis of elevated marker, but the marker failed to reveal two out of three relapses. The patient sensitivity of the Ca 15-3 test here was 36% and test sensitivity was even lower at 13%.

In the aforementioned study by Bombardieri and colleagues [5], Ca 15–3 patient specificity was 97% and according to Molina and colleagues [9] it was 99%, using a cut-off value of 60 U/ml in the test assay, and probably because of the higher cut-off level, the specificity was very high. Patient specificity of the Ca 15-3 test in our study was high at 97%, and test specificity was 99%.

In the present series, the positive predictive value of Ca 15-3 test was 78% (relapses). Söletormos and colleagues [8] found the negative predictive value of CA 15-3 for breast cancer patients with bony and visceral metastases to be 86%, in other words, with a negative Ca 15-3 value, it was very unlikely that the breast cancer patient had metastases in the bone/viscera. The negative predictive value of Ca 15-3 of 82% was here slightly better than the positive predictive value of the test and approximately the same as in the study by Söletormos and colleagues. Negative test results ruled out recurrent disease reasonably well with an 82% probability.

We found Ca 15-3 values to be elevated in 21/59 patients (36%) with recurrent disease in routine scheduled follow-up. As in the published literature, we found that marker values were more often above the reference area in multiple or liver metastatic disease, where the tumour burden is considered to be heavy: in all four liver-only metastases and in approximately half of the multiple or bone-only metastasis values were high. Söletormos's group [8] discovered that elevated Ca 15-3 test correctly classified 48% of breast cancer patients with metastases in bone/viscera, and during the follow-up time of 18 months after Ca 15-3, 100% of patients developed metastases in the bone/viscera. The cut-off value was 30 IU/l.

Berruti and colleagues [3] likewise found higher marker levels for patients with pulmonary/pleural-only metastases. In contrast, we found no elevated marker values in pulmonary-only metastases, but there were only 5 such cases and no pleural-only metastases in our patients. Molina and associates [9], also have found low Ca 15-3 sensitivity in detecting lung metastases in breast cancer patients. Ca 15-3 is usually not elevated in new contralateral breast cancer [5,7,12]. This was also the case in the present study: in the three contralateral breast cancers, marker values were within the reference area.

Use of the Ca 15-3 test in the follow-up of breast cancer might involve a considerable risk of overdiagnosis and lead time. When the test result is positive and there is no other confirmation of metastatic disease, decision-making is difficult as to whether to treat or not. According to Geraghty and associates [12], the mean lead time to diagnosis of metastases in patients with rising Ca 15-3 was 9.5 months, in the study by Söletormos and colleagues [8] it was only 64 days, and according to Molina and colleagues [9] about 4.2 months. The mean lead time in our study was 89 days, less than 3 months, but the median lead time was only 18 days. Therefore, there is a chance that the quality of life might be impaired because of psychological fear and anxiety.

In conclusion, our study is consistent with the American Society of Clinical Oncology (ASCO) recommendations [1,2,11]. The tumour marker, Ca 15-3, could be used with a fairly high probability to rule out relapsing

breast cancer with multiple sites or liver metastases, since the test specificity was good. Only one-third of all breast cancer recurrences were found by tumour marker Ca 15-3. However, Ca 15-3 is only one breast cancer marker among many others [13,14]. Addition of some other markers such as carcinoembryonic antigen (CEA), or the erythrocyte sedimentation rate (ESR) can raise the sensitivity of the serum marker testing in breast cancer considerably.

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