Comparison of bone scintigraphy with serum tumor markers of CA 15–3 and carcinoembryonic antigen in patients with breast carcinoma

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ABSTRACT

Objectives: To compare the bone scintigraphy findings with a carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA 15-3) levels in breast carcinoma patients. We also investigated the relationship between anatomical bone type and its effect on tumor marker levels.

Methods: The study was consisted of retrospective evaluation of 120 bone scans of patients with breast carcinoma admitted to the Nuclear Medicine Department, Medical Faculty, Hacettepe University, Ankara, Turkey between January 2003 and December 2004. The mean age of the patients was 54.7 years. We grouped the results of the bone scans into 3 as normal, equivocal and metastatic. Carcinoembryonic antigen and CA 15-3 levels were recorded from the files of the patients. Upper cut levels of 4.8 U/ml for CEA and 38 U/ml for CA 15-3 was accepted. Metastatic bone areas were distributed according to their anatomical location as long, short, flat, irregular and sesamoid and effect of bone type on tumor marker was investigated.

Results: In 16 of the patients, bone scintigraphy revealed metastases. Sixty-one patients had normal scans and in 47 patients metastases could not be ruled out. In patients with metastases, CA 15-3 was elevated in 8 and CEA was higher than the upper limit in 6. For CEA and CA 15-3, the anatomical type of bone has no any effect on serum tumor marker concentration between patients with normal and elevated levels of tumor markers in metastatic patients.

Conclusion: Tumor markers are not solely enough in predicting bone metastases. Bone scintigraphy and tumor markers should be both used in management of patients with breast carcinoma. The anatomical type of bone has no any effect on elevation of serum tumor marker concentration.

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Breast carcinoma is a serious health problem throughout the world with approximately more than 700,000 patients are being diagnosed every year.[1] Determining the prognostic factors such as tumor size, vascular invasion, presence of lymph node or distant metastases play a great role in the management of patients with breast carcinoma.[2] Among these, extension of the disease is the most important and treatment with prognosis is mostly related to the metastatic spread of the cancer.[3] Breast cancer can and frequently does metastasize to almost every organ in the body but the skeleton is the most frequent target.[4] The detection of bone metastases has both prognostic and therapeutic significance, where patients with bone metastases

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have a mean survival of 2 years.[5] While being the most frequent site for metastases, the skeleton is also affected by chronic degenerative, inflammatory and metabolic lesions of bone which can be investigated with bone scintigraphy.[6] However, abnormal bone scan appearance in bone scintigraphy is not specific and altered bone metabolic activity whether secondary to neoplastic or benign process will lead to abnormality on bone scan. The recently developed imaging modalities such as computerized tomography (CT) and magnetic resonance imaging (MRI) can also be used to monitor bone lesions, but widespread using of these techniques in all patients is limited by their expensive and time-consuming nature. For that reason, detecting the progression of the tumor by substances so called tumor markers can be considered to identify patients with aggressive disease and indolent course. Carcinoembryonic antigen (CEA) and the cancer antigen 15-3 (CA 15-3) are the most frequently used markers for evaluating and monitoring the patients with breast cancer.[7] The CA 15-3 is considered to be more specific than CEA for monitoring and early detection of recurrences in breast cancer.[7] However, elevation of their levels does not always prove the presence or progression of the disease. The aim of this study is to investigate the role of tumor markers and bone scintigraphy in patient's follow up and to compare these techniques in terms of tumor progression in patients with breast carcinoma. Besides, the effect of which type of bone involved in the metastatic process on serum tumor marker concentration was also investigated.

Methods. Between January 2003 and December 2004, bone scans of 120 patients with histologically proven breast carcinoma were retrospectively investigated. The mean age of the patients was 54.7 years (range of 26-86 years). Bone scans were performed 3-4 hours following intravenous injection of 555-740 MBq (15-20 mCi) of technetium 99m methylene diphosphonate (99mTc-MDP) using a gama camera equipped with a low energy, high resolution collimator (General Electric, Infinia and ADAC, Philips). The photopeak was centered at 140 keV with a 20% window. The bone scans were evaluated by 2 experienced nuclear medicine physicians. The results of other imaging modalities such as CT and MRI were also reviewed if available and at the end, the scans were distributed into 3 groups such as; normal, equivocal and metastatic in origin. The principle criteria for interpretation of the bone scans were as follows: (i) Findings which are likely not due to bone metastases; normal bone scans, no hot spot, one or more hot spots in regions where degenerative changes are frequently observed (**Figure 1**). (ii) Findings which are suspicious about bone scans; equivocal bone scans, one or more hot spots in regions that are unusual for benign lesions and asymmetry of tracer uptake in where radiologic comparison was not available (**Figure 2**). (iii) Findings very likely due to bone metastases; metastatic bone scans, multiple obvious hot spots or single hot spot with intense radiotracer uptake and radiologic correlation which also reveals metastases (**Figure 3, Figure 4**). In the next step, the bones in the metastatic scans were distributed according to their anatomical types such as long, short, flat, irregular and sesamoid. In this classification: femur, tibia, fibula, humerus, radius and ulna were termed as long; clavicula, all metacarpals, phalanges of hand and feet and all metatarsals were termed as short; scapula, all ribs, sternum, pelvic bones and the bones in calvarium were termed as flat; carpal, tarsal and the entire vertebral column were termed as irregular and patella was termed as sesamoid bone.[8,9] Each patient with a metastatic bone scan, took a score for each type of bone according to the number of involved bones from each type in the metastatic process. If a joint such as sacroiliac is involved, then the patient took a score for both bone types in the joint. The serum concentrations of CA 15-3 and CEA were retrieved from the patients' files where the techniques to measure CEA and CA 15-3 were same for all patients. The serum CEA and CA 15-3 levels were determined by the electrochemiluminesance immunoassay (ECLIA) method with Roche Elecsys Analytics. The normal upper value given from our laboratory was 4.8 U/ml for CEA and 38 U/ml for CA 15-3. The results of bone scans were compared with the tumor marker levels. If the patient had a bone scan both at the diagnosis and after treatment the bone scans were also compared with the progress of the levels of tumor markers. In patients with bone metastases, the effect of anatomical type of bone on serum tumor marker concentrations between the patients who have normal and who have elevated levels were investigated by Mann-Whitney U test. The difference was regarded as statistically significant when p values were <0.05. All calculations were performed with SPSS for windows.

Results. The scintigraphic studies showed 16 patients had bone scans concordant with metastases. Sixty-one of them had normal scans and in 43 patients metastases could not be ruled out, and the results of the scintigraphy were equivocal. Out of 120 patients, 17 had elevated levels of CA 15-3 (14%) whereas CEA levels were elevated in 16 patients (13%). The results of bone scans, and tumor marker levels are given in

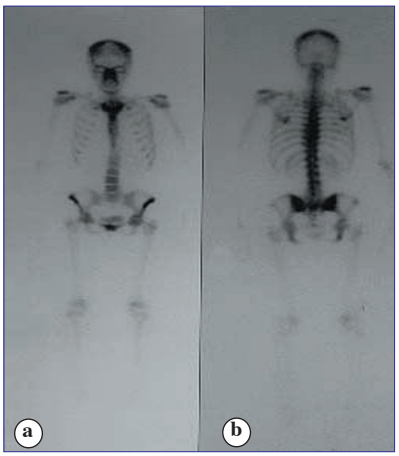

Figure 1 - A 32-year-old patient who was suffering from breast carcinoma was investigated for bone metastases. **a)** Her cancer antigen 15-3 level was higher than the cut-off level (41.82 U/ml) and bone scintigraphy was normal (anterior view). **b)** She was investigated for bone metastases one year later with bone scintigraphy and the scan was normal (posterior view).

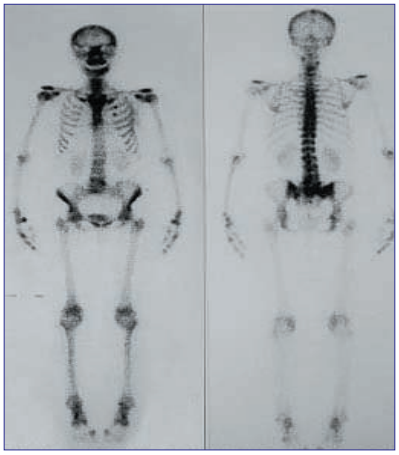

Figure 2 - A bone scan of a 80-year-old patient with breast carcinoma showed rib lesions in the second, third and fourth anterior ribs in the left side. She also had increased radioactivity in cervical and lumber vertebras. She did not have a trauma history so although degenerative changes were thought in her cervical and lumbar regions, radiologic correlation was not available and metastases could not be ruled out in ribs.

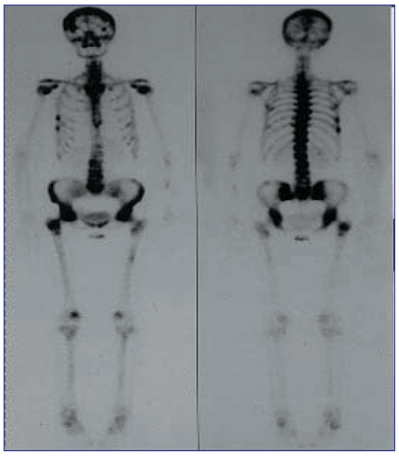

Figure 3 - A 53-year-old patient with breast carcinoma was referred for bone scan. Her cancer antigen 15-3 level was within normal limits (25.47 U/ml) and the scintigraphy showed multiple metastases (patient 3).

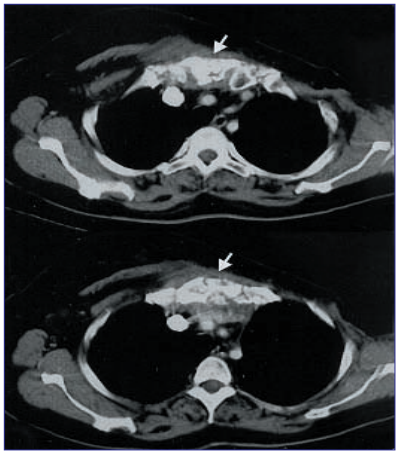

Figure 4 - A 44-year-old patient who had been followed for breast carcinoma had gone through bone scintigraphy. Her bone scan showed increased radioactivity in sternum. Computerized tomography revealed metastatic destruction in sternum (arrow) (patient one).

Table 1 - Comparison of bone scintigraphy and tumor marker levels

Bone scintigraphy	Carcinoembryonic antigen (U/ml)		Cancer antigen 15-3 (U/ml)	
	Normal	Elevated	Normal	Elevated
Metastatic	10	6	8	8
Normal	55	6	58	3
Equivocal	39	4	37	6
Total	**104**	**16**	**103**	**17**

Table 2 - Tumor marker values and bone type scores in metastatic patients

Patient no.	CA 15-3 (U/ml)	CEA (U/ml)	Long bone score	Short bone score	Flat bone score	Irregular bone score	Sesamoid bone score
1	29.74	2.93	0	0	1	0	0
2	21.47	3.67	0	0	2	1	0
3	25.47	5.36	3	0	7	3	0
4	29.73	3.99	0	0	2	0	0
5	26.11	2.69	1	0	1	2	0
6	24.96	2.76	0	0	6	6	0
7	22.88	1.45	0	0	5	9	0
8	14.04	3.64	2	0	2	2	0
9	45.92	3.63	1	1	9	8	0
10	133.8	4.44	1	0	11	5	0
11	138	7.22	1	0	7	4	0
12	66.5	73	1	0	10	5	0
13	207.6	80.41	1	0	3	2	0
14	43.27	5.03	0	0	2	1	0
15	40.52	11.4	0	0	1	1	0
16	367.1	4.35	1	0	4	4	0

CA 15-3 - cancer antigen 15-3, CEA - Carcinoembryonic antigen

Table 1. While in patients with bone metastases, the sensitivity of CA 15-3 level was 50% and CEA level was 37%, among patients without bone metastases, normal values of CA 15-3 and CEA present a specificity of 95% and 90%. In 8 patients who had a bone metastases but had normal CA 15-3 levels, serial serum measuring showed elevation of CA 15-3 concentration in 2 of them, but remained normal in 6. No elevation of CEA levels was observed in 9 out of 10 patients who had bone metastases but in one of them the serial measuring revealed an elevation. Among 3 patients who had elevated levels of CA 15-3 but with normal bone scans, the marker levels turned to normal limits in 2 of them while the remaining one patient had no any serial serum marker evaluation. Carcinoembryonic antigen levels continued to show abnormality in 4 of 6 cases who had normal bone scans, one patient did not have serial examination and the remaining one had normal CEA levels in further evaluations. The 6 patients who had elevated CEA levels with normal bone scans, were also evaluated by CT and ultrasonography, one of them had pulmonary metastases which were shown in CT and one patient had no any sign of distant metastases. Amongst 16 patients with metastatic bone scans, flat and irregular types of bones were the most involved bones in the metastatic process (**Table 2**). Of the 16 patients with metastatic bone scans 11 had multiple hot spots in the bone scan and 5 had one to three lesions with low bone scores (**Table 2**). When CA 15-3 was considered, the anatomical type of bone had no effect on serum tumor marker elevation between patients who had normal and who had elevated levels in metastatic group. The calculated probability value for long bone was p=0.491, short p=0.317, flat p=0.137 and irregular bone was p=0.397. For CEA the difference was not significant (long p=0.476, short p=0.439, flat p=0.622 and irregular p=0.662).

Discussion. Breast carcinoma is the most life threatening malignant lesion in women in many developed countries. It is the most frequent cause of death in women aging 35-54 years.[10] Prognosis is strongly related with the extent of the disease so patient monitorization is especially important in the management of patients with breast carcinoma. CA 15-3 and CEA are the tumor markers which provide evidence on the likelihood of undiagnosed cancer or the status of the treated cancer in patients with breast carcinoma. Bone scintigraphy is another tool used in the management of breast carcinoma with high sensitivity but limited specificity that may demonstrate hot spots in patients who remain disease free. Without the expense and discomfort of the imaging modalities, CA 15-3 and CEA are questioned whether they are able to substitute directly for a bone scan has been an area of investigation. Yıldız et al[2] reported that it is not justifiable to reject a bone scan on the basis of

the markers. Buffaz et al[3] found that CA 15-3 assay can be a guide in the prescription of bone scan and normal CA 15-3 level allows deferment of the bone scan. In our study there were 16 patients with bone metastases in which 8 of them had elevated levels of CA 15-3 whereas CEA levels were elevated in only 6 of them. In the current literature, CA 15-3 and CEA were investigated in terms of their usefulness for screening, indicator of asymptomatic recurrence or monitoring response to treatment[11] and CA 15-3 was reported to be more sensitive than CEA in the detection of metastases.[12] In agreement with the other studies, our study also showed that CA 15-3 is more sensitive than CEA when metastases are discovered. However, CA 15-3 levels were normal in 8 and CEA levels were normal in 10 of 16 metastatic patients. Among these, 5 of 8 patients with a normal CA 15-3 and 7 of 10 patients with a normal CEA had previously received chemotherapy. This may explain the normal marker levels but also makes them inadequate to predict the bone scan result. In the 10 patients with normal CEA levels but metastatic scans, only one of them showed an elevation and 9 had CEA levels within normal limits in further examinations. CA 15-3 levels were also in normal limits in 6 of 8 patients with bone metastases and in 2 there was an elevation in further examinations. Crippa et al[13] and Yıldız et al[2] reported the importance of the number of lesions in bone scans with relatively lower sensitivity of CA 15-3 in patients with a small number of lesions. In our study, 5 of 8 patients (62.5%) who had normal CA 15-3 levels but with metastatic scans and 7 of the 10 patients (70%) with normal CEA levels but metastatic scans had multiple lesions in their scintigraphies. Since in metastatic group, more than half of the patients with normal levels CA 15-3 and CEA had multiple number of lesions, our results are discordant with the other studies which attribute the lower sensitivity of tumor markers to the number of lesions in bone scans. Why tumor markers elevate in some of the metastatic patients and why do not in some of them is not well understood yet. It is well known that bone metastases occurs by hematogenous dissemination and axial skeleton is influenced more than the appendicular skeleton.[14] Although there are 5 types of anatomically classified bones, structurally there are only 2 type of bones: compact and spongy. The compact bone is strong and dense having no spaces within it. The osteons in compact bones align in the same way, increases the resistance to the stress applied along the axis of alignment. Spongy bones however have numerous spaces within, showing the same histology as compact bones. Although spongy bone is more metabolically active than compact bone due to its much larger surface area for remodeling, the localization of compact and spongy bones shows no difference between the different types of bones. Usually, all types of bones are sandwiches of spongy bone between 2 layers of compact bone. So although our study had limited number of patients with metastases, the anatomical type of bone does not seem to be the cause of not elevation of tumor markers in some patients. Our study was not planned prospectively, and not every equivocal bone scan received radiologic correlation. So we could not definitely investigate the role of tumor markers as a guide for selecting patients with skeletal metastases. The 6 patients with elevated levels of CEA and normal bone scans, 4 continued to have higher serum concentrations in further evaluations. But, CA 15-3 decreased to normal levels in 2 of the 3 patients with normal bone scans. Carcinoembryonic antigen is overexpressed in different types carcinomas, besides elevated levels of CEA accompany non-neoplastic inflammatory diseases such as cirrhosis, cholelithiasis, gastritis and collagen vascular diseases.[3] These patients were also evaluated with ultrasonography and computerized tomography, and only one of them had pulmonary metastases, we considered the other one as disease free and we postulated that CA 15-3 is a more specific tumor marker compared to CEA, conforming with other studies.[15] Besides from their known-limited role in local or primary breast carcinoma, our data suggest that CEA and CA 15-3 should also have limited utility in predicting bone metastases. A normal tumor marker level must not only be taken into consideration and patients must also be evaluated with bone scintigraphy. The anatomical type of bone does not have any effect on elevation of serum tumor marker, and some other reasons must be investigated in further studies with larger number of patients.

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