Annals of Nuclear Medicine Vol. 18, No. 6, 501–505, 2004

Relationship between bone scintigraphy and tumor markers in patients with breast cancer

Mustafa YILDIZ,* Baha ORAL,** Mehmet BOZKURT*** and Azem COBANER****

*Department of Nuclear Medicine, Süleyman Demirel University, School of Medicine, Isparta, Turkey
**Department of Obstetrics and Gynaecology, Süleyman Demirel University, School of Medicine, Isparta, Turkey
***Isparta State Hospital, General Chirurgia, Isparta, Turkey
****Sinyal Nuclear Medicine Center, Antalya, Turkey

Purpose: The aim of this study is to specify the precise role of bone scintigraphy and serum CEA and CA 15-3 assays in the monitoring of breast cancers in order to optimize their use and to determine whether it is possible to guide the prescription of bone scan by the use of CEA and CA 15-3 assays in the monitoring of breast cancer. ***Methods:*** For this purpose, from November 1997 to May 2002, 98 consecutive female breast cancer patients (median age, 52 years; range 35–77 years) underwent bone scintigraphy during follow-up. In these patients values of tumor markers were compared with the results of bone scintigraphy. Some of the patients with bone metastasis were checked repeatedly at intervals of 6 to 12 months, resulting in 49 patients with bone metastasis and 74 patients without bone metastasis being included in the study. ***Results:*** In patients with bone metastasis, serum CEA levels were abnormal in 23/49 cases and CA 15-3 serum concentrations were elevated above the cut-off in 33/49 cases. Among patients without bone metastasis, CEA and CA 15-3 serum concentrations were normal in 50/74 and 55/74 cases respectively. The combination of the two markers improved the diagnostic sensitivity. ***Conclusion:*** Although serial tumor marker measurements are an efficient and cost effective method of monitoring disease progression, it does not allow prediction of the bone scan results; so it is not justifiable to reject a bone scintigraphy on the basis of these markers.

Key words: breast cancer, bone scintigraphy, carcinoembryonic antigen (CEA), breast cancer-associated antigen (CA 15-3)

INTRODUCTION

BREAST CANCER is a significant health problem worldwide. It kills more women than any other malignant tumor. The prognosis depends on many factors such as tumor biology, histology, peritumoral vascular invasion, tumor size, lymph node involvement, receptor status and presence of distant metastasis. The skeleton is the most frequent site of metastasis in breast cancer.[1]

Bone scintigraphy with Tc-99m diphosphonates has a high sensitivity; however, it also has a low specificity and may demonstrate hot spots in those patients who remain permanently disease-free.[2] It is not feasible to perform this examination systematically for the diagnosis and follow-up of every cancer patient.

Tumor markers whose blood levels seem to correlate with the tumor mass are useful tools both in the diagnosis and follow-up of certain cancers. In recent decades, tumor markers such as carcinoembryonic antigen (CEA) and breast cancer-associated antigen CA 15-3 have been used as a warning sign of distant metastasis of breast cancer.[3–7]

The aim of the current study was to specify the precise role of these two different tools within diagnostic policies in the monitoring of breast cancers in order to optimize their utility and to determine whether it is possible to guide the prescription of bone scan by the use of CEA and CA 15-3 assays in the monitoring of breast cancer.

Received February 17, 2004, revision accepted May 17, 2004.
For reprint contact: Mustafa Yildiz, M.D., Istiklal Mah., Güven Cad., 38/8, 32100, Isparta, TURKEY.
E-mail: mustiyildiz01@superonline.com

MATERIALS AND METHODS

Patients

From November 1997 to May 2002, 98 consecutive female breast cancer patients (median age, 52 years; range 35–77 years) underwent bone scintigraphy during follow-up. All patients had a diagnosis of breast cancer confirmed histopathologically (75 cases of ductal carcinoma, 10 cases of lobular carcinoma, 5 cases of tubular carcinoma, 4 cases of mucinous carcinoma, and 4 cases of medullary carcinoma) and underwent different treatments consisting of combined chemotherapies, various hormone therapies, and/or radiotherapy depending on the pathological stage and prognostic factors. Modified radical mastectomy (MRM) was performed in 57 patients with clinical stage II and III. Adjuvant chemotherapy was offered to the patients with stage II disease. Patients with stage IIIA disease received adjuvant chemotherapy following surgery. Patients with stage IIIB or IIIC disease who responded to primary chemotherapy underwent definitive surgery and irradiation. Forty-one patients with stage IV disease received chemotherapy and radiotherapy for painful bone lesions. Tamoxifen for 5 years was recommended to patients whose tumors are hormone responsive. There were 66 patients without bone metastasis (median age, 52 years; range 35–77 years) and 32 patients with bone metastasis (median age, 52 years; range 34–75 years). In these patients, values of tumor markers were compared to the results of bone scintigraphy. Some of the patients with bone metastasis were checked repeatedly at intervals of 6 to 12 months, resulting in 49 patients with bone metastasis and 74 patients without bone metastasis being included in the study.

Tumor markers

The techniques to measure CEA and CA 15-3 concentrations were the same for all patients. The serum CEA and CA 15-3 concentrations were determined by the electrochemiluminescence 'ECLIA' method on a Roche Elecsys 2010 analyzer.[8] Serum CEA and CA 15-3 levels of 4.6 ng/m*l* and 22 U/m*l*, respectively, were adopted as the upper limits of normal. In combined use of two tumor markers, we classified patients into "tumor marker positive group" if at least one of these markers exceeded its cut-off level.

Bone scintigraphy

Bone scans were performed 2–4 hours following i.v. injection of 555–740 MBq (15–20 mCi) of technetium-99m methylene diphosphonate (^{99m}Tc-MDP) using a gamma camera with a low energy, high resolution collimator (General Electric AC/T or Toshiba GCA-901/SA). The photopeak was centered at 140 keV with a 20% window in cameras. The bone scans were evaluated by two experienced observers. They were judged as negative or positive for bone metastasis. Bone metastasis-positive studies were divided based on metastatic tumor burden by bone scan and other correlative methods such as plain X-ray, computed tomography (CT), and magnetic resonance imaging (MRI). The metastatic tumor burden was judged as follows: grade 1, single lesion; grade 2, two to five lesions; grade 3, more than six lesions.[9]

Statistical analysis

Data were analyzed using the statistical software program SPSS for Windows version 9.05 (SPSS Inc., Chicago, IL). Results were given as the mean ± SD. Statistical significance was set at the 0.05 level. The groups were compared using the Student's t test and Mann-Whitney test as appropriate. The scintigraphic subgroups were compared using one-way ANOVA followed by Tukey's method.

Table 1 Distribition of patients with and without bone metastasis with respect to the cut-off level of CEA

	CEA > 4.6 ng/m*l*	CEA < 4.6 ng/m*l*	Sum
Metastasis (+)	23	26	49
Metastasis (–)	24	50	74
Sum	47	76	123

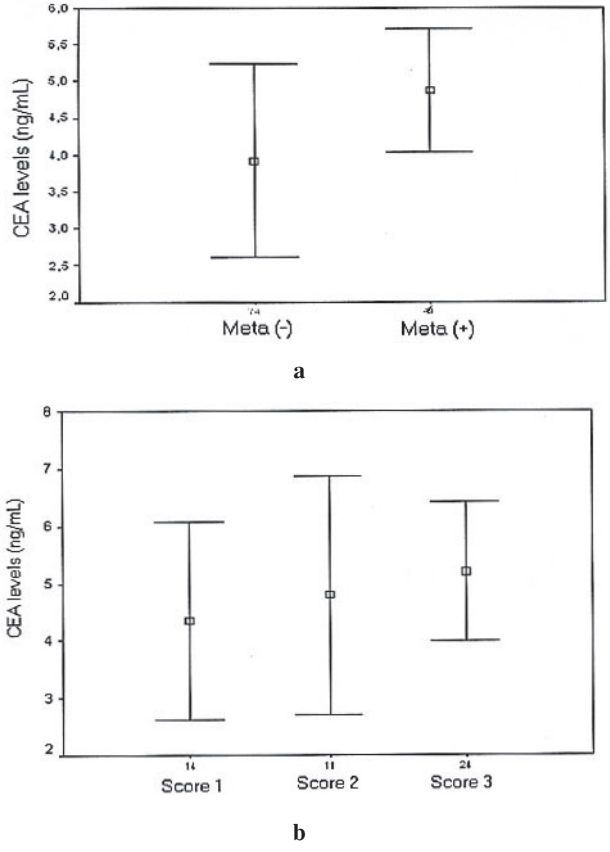

Fig. 1 a: CEA levels in relation to the bone metastasis status of the patients. b: CEA levels in relation to the bone scan results.

Table 2 Distribution of patients with and without bone metastasis with respect to the cut-off level of CA 15-3

	CA 15-3 > 22 U/m*l*	CA 15-3 < 22 U/m*l*	Sum
Metastasis (+)	33	16	49
Metastasis (–)	19	55	74
Sum	52	71	123

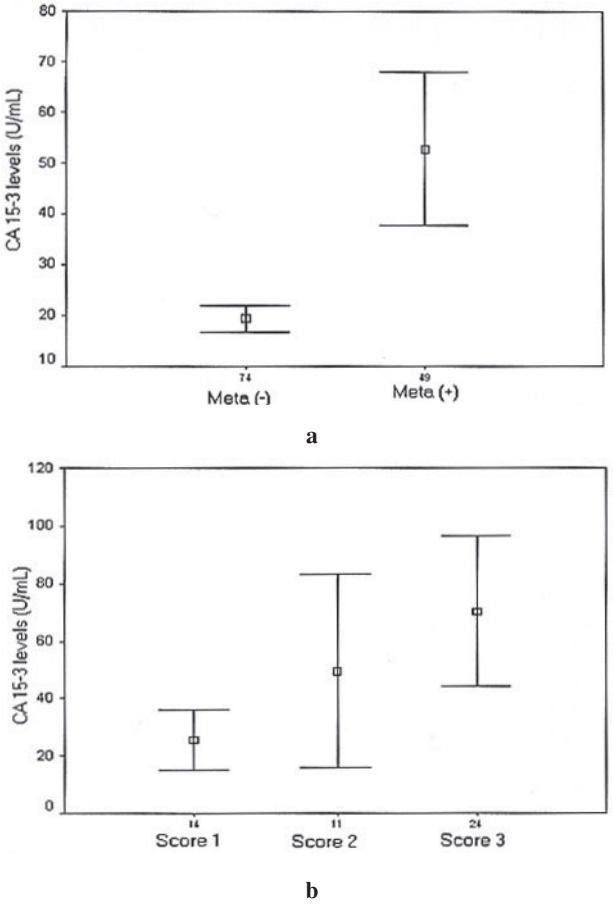

Fig. 2 a: CA 15-3 levels in relation to the bone metastasis status of the patients. b: CA 15-3 levels in relation to the bone scan results.

RESULTS

In patients with bone metastasis, CEA levels were abnormal in 23/49 cases (sensitivity for bone metastasis = 47%). Among patients without bone metastasis, CEA serum concentrations were normal in 50/74 cases (specificity = 67%) (Table 1). The positive predictive value for bone metastasis was 48% and the negative predictive value was 65%. Figure 1a summarizes the CEA levels in relation to the bone metastasis status of the patients. CEA levels in relation to the bone scan results are shown in Figure 1b. No significant difference (p = 0.36) was found in the average levels of CEA in relation to the bone scan results.

In patients with bone metastasis CA 15-3 serum concentrations were elevated above the cut-off in 33/49 cases (sensitivity for skeletal metastasis = 67%). Among patients without bone metastasis, CA 15-3 serum concentrations were normal in 55/74 cases (specificity = 74%) (Table 2). The positive predictive value for bone metastasis was 63% and the negative predictive value was 77%. Figure 2a shows the CA 15-3 levels in relation to the bone metastasis status of the patients. Sixteen of 71 patients with a CA 15-3 level of less than 22 U/m*l* and 26 of 76 patients with a CEA level of less than 4.6 ng/m*l* during follow-up had a bone scan which revealed the presence of bone metastasis. When the scans were positive for the presence of bone metastasis (49 individuals), the CA 15-3 level 52.83 ± 53.26 U/m*l*. By contrast, when the scans were negative for the existence of bone metastasis (74 eases), CA 15-3 level was 18.11 ± 10.89 U/m*l*, a very significant difference (p = 0.0001). Figure 2b shows CA 15-3 levels in relation to the bone scan results. A statistically significant difference (p = 0.001) was found in the average levels of CA 15-3 in relation to the bone scan score results.

The combination of the two markers showed a sensitivity of 73.5% in revealing bone metastasis. Among patients without bone metastasis CEA and/or CA 15-3 serum concentrations were normal in 44/74 cases (specificity = 59.5%). The positive predictive value for bone metastasis was 54.5% and the negative predictive value was 77.2%.

DISCUSSION

Bone metastasis is very common event in patients with breast cancer, and there is need for early detection and monitoring of bone metastasis. Post-mortem studies have shown that bone metastasis was present in 47%–85% of women who died of breast cancer.[10] The clinical oncologist who cares for breast cancer patients following mastectomy frequently faces the clinical problem of how to differentiate between benign and metastatic skeletal lesions.

Bone scintigraphy, which is employed for this purpose, has remarkable sensitivity for the detection of bone metastasis, but its specificity without other correlative imaging or interval follow-up is relatively poor. Focally increased osteoblastic activity is not specific to metastasis, and other focal disorders such as osteoarthritis or rib fractures may cause diagnostic difficulty by producing similar bone scan appearances.[11]

CEA and CA 15-3 have been used in the diagnosis of breast cancer and detection of distant metastasis including bone. Determination of CEA and CA 15-3 serum concentrations in association with bone scintigraphy could improve the diagnosis of bone metastasis in breast cancer patients. CEA is a glycoprotein, which is a normal cell product overexpressed in different types of carcinomas. Levels of this tumor marker can be elevated in various non-neoplastic inflammatory diseases like liver cirrhosis,

cholelithiasis, emphysema, bronchitis, gastritis, collagen vascular diseases and others. CA 15-3 is a glycoprotein, which is normally expressed on the apical surface of epithelial cells in the duct and the acini of breast and excreted in the milk. In breast cancer, the normal tissue architecture is disrupted, and therefore CA 15-3 is shed in to the blood-stream.[12]

Zanco et al. investigated 147 patients after surgical removal of breast cancer.[5] They reported a sensitivity of 39% for CEA and 65% for CA 15-3 in predicting metastasis. The combination of the two markers showed a sensitivity of 69%. Crippa et al. found CA 15-3 levels to be abnormal in 59/85 cases (sensitivity for bone metastasis = 69.4%).[3] They reported the positive predictive value for bone metastasis to be 50.4% and the negative predictive value 96%. A very limited sensitivity (33.3%) was described in patients with only one or two bone metastasis sites. The sensitivity was reported to be 86.1% when the number of metastatic sites was more then six. Nicolini et al. investigated 297 breast carcinoma patients postoperatively.[4] Patients were followed by CEA, tissue polypeptide antigen (TPA) and CA 15-3 measurements at 6 or 4 month intervals and bone scintigraphy at a 24 month interval. Eighteen (87%) of the 22 patients with bone metastasis showed constant elevation or progressive increase on the tumor marker panel. Tumor marker panel specificity was 96% on the basis of their results; the authors concluded that tumor markers in the follow-up can be suitable in selecting patients who should undergo further radiological examinations.

In our study, eleven of 16 patients with a normal CA 15-3 and 18 of 26 patients with a normal CEA were receiving or had previously received chemotherapy (which could explain the normal marker levels). These results suggest that normal CA 15-3 and CEA levels in a patient with breast cancer do not allow deferment of a bone scintigraphy.

Safi et al. measured CA 15-3 and CEA in 671 patients who had received initial curative surgery of breast cancer and who regularly attended their follow-up clinic.[13] They found CA 15-3 to be more sensitive than CEA in detecting recurrences of breast cancer. In the postcare period CA 15-3 had a sensitivity of 73% and CEA had a sensitivity of 50% in detecting recurrences. They concluded that CA 15-3 was significantly better than CEA in the detection of breast cancer metastasis.

Kokko et al. reported that CA 15-3 levels were elevated in half of bone metastasis.[7] In a retrospective study, Younsi et al. found normal CA 15-3 levels and bone metastasis in 4% of patients in a group of 157 patients with breast cancer.[15] Crippa et al. attributed the lower sensitivity of CA 15-3 for bone metastasis to the relatively high number of false negative results observed in patients with a small number of lesions.[3] In our study, all of the patients with normal CA 15-3 and CEA levels but having bone metastasis had a bone scan score of 1. The specificity of CA 15-3 was nonsignificantly higher than the specificity of CEA (74% vs. 67%, $p = 0.45$) in our study. This means that 19 patients in CA 15-3 panel and 24 patients in CEA panel were found to be assay positive although bone metastases were not present. CEA is a glycoprotein that is overexpressed in different types of carcinomas. Levels of this tumor marker can be elevated in various non-neoplastic inflammatory diseases as well as organ metastasis other than to the skeleton.

The rates of abnormal values of CA 15-3 and CEA, and the mean values of CA 15-3 and CEA serum concentrations increased in relation to the number of skeletal lesions. In patients with a bone scan score 1, CA 15-3 was >22 U/m*l* in 6/14 cases (42%) and the mean serum concentration was 25.62 ± 18.12 U/m*l*. In patients with a bone scan score of 3, these figures rose to 20/24 (83%) and 70.24 ± 62.29 U/m*l* respectively. In patients with a bone scan score of 1, CEA was > 4.6 ng/m*l* in 5/14 cases (35%) and the mean serum concentration was 4.35 ± 2.98 ng/m*l*; in patients with a bone scan score 3, these figures rose to 13/24 (54%) and 5.19 ± 2.87 ng/m*l* respectively. The rises in CA 15-3 panel were statistically significant ($p = 0.02$ and $p = 0.01$, respectively) whereas the rises in CEA panel were not ($p = 0.41$ and $p = 0.39$, respectively). These results agree with published data which show a good correlation between the number of sites of bone involvement and serum CA 15-3 and CEA levels.[3]

Buffaz et al. reported a strong correlation between CA 15-3 levels and bone scan findings.[14] Our results are in accordance with these findings. We found serum CA 15-3 concentration to be 52.83 ± 53.26 U/m*l* in patients with a positive bone scan and 18.11 ± 10.89 U/m*l* in patients with a negative bone scan ($p = 0.0001$).

The above findings allow us to draw the following conclusions. The sensitivity of CA 15-3 determination for the diagnosis of bone metastasis in breast cancer patients is reduced by false-negative results in patients with a low bone scan score. CA 15-3 showed higher sensitivity for bone metastasis than CEA. CA 15-3 is also more specific than CEA. Although the demonstration of elevated levels of CA 15-3 makes the diagnosis of skeletal metastasis reasonable, it does not allow prediction of the bone scan result; so is not justifiable to reject a bone scintigraphy on the basis of these markers. These studies should attempt, in addition, to set a suitable threshold; in our study the normal upper value given by the laboratory (22 U/m*l*) was arbitrarily chosen as the threshold for CA 15-3, in the same way as 4.6 ng/m*l* was chosen as the threshold for CEA. Although serial tumor marker measurements are an efficient and cost-effective method of monitoring disease progression, our group of patients was too small to make our observation conclusive.

REFERENCES

1. Coleman RE, Rubens RD. The clinical course of bone

metastasis from breast cancer. *Br J Cancer* 1987; 55: 61–66.
2. Coleman RE, Rubens RD, Fogelman I. Reappraisal of the baseline bone scan in breast cancer. *J Nucl Med* 1988; 29: 1045–1049.
3. Crippa F, Bombardieri E, Seregni M, et al. Single determination of CA 15.3 and bone scintigraphy in the diagnosis of skeletal metastasis of breast cancer. *J Nucl Biol Med* 1992; 36: 52–55.
4. Nicolini A, Ferrari P, Sagripanti A, Carpi A. The role of tumour markers in predicting skeletal metastasis in breast cancer patients with equivocal bone scintigraphy. *Br J Cancer* 1999; 79: 1443–1447.
5. Zanco P, Rota G, Sportiello V, et al. Diagnosis of bone and liver metastasis in breast cancer comparing tumor markers and imaging techniques. *Int J Biol Markers* 1989; 4: 103–105.
6. O'Brien DP, Horgan PG, Gough DB, et al. CA 15-3: a reliable indicator of metastatic bone disease in breast cancer patients. *Ann R Coll Surg Engl* 1992; 74: 9–11.
7. Kokko R, Holli K, Hakama M. Ca 15-3 in the follow-up of localised breast cancer: a prospective study. *Eur J Cancer* 2002; 38: 1189–1193.
8. Forest JC, Masse J, Lane A. Evaluation of the analytical performance of the Boehringer Mannheim Elecsys 2010 immunoanalyzer. *Clin Biochem* 1998; 31 (2): 81–88.
9. Koizumi M, Yamada Y, Takiguchi T, et al. Bone metabolic markers in bone metastasis. *J Cancer Res Clin Oncol* 1995; 121: 542–548.
10. Tubiana-Hulin M. Incidence, prevalence and distribution of bone metastasis. *Bone* 1991; 12: 9–10.
11. Cook GJR, Fogelman I. Skeletal metastasis from breast cancer: Imaging with Nuclear Medicine. *Semin Nucl Med* 1999; 29: 69–79.
12. Clinical practice guidelines for the use of tumor markers in breast and colorectal cancer. Adopted on May 17, 1996 by the American Society of Clinical Oncology. *J Clin Oncol* 1996; 14: 2843–2877.
13. Safi F, Kohler I, Rottinger E, Beger H. The value of the tumor marker CA 15-3 in diagnosing and monitoring breast cancer. A comperative study with carcinoembryonic antigen. *Cancer* 1991; 68: 574–582.
14. Buffaz PD, Gauchez AS, Caravel JP, et al. Can tumor marker assays be a guide in the prescription of bone scan for breast and lung cancers? *Eur J Nucl Med* 1999; 26: 8–11.
15. Younsi N, Montravers F, Philippe C, et al. CA 15-3 and bone scintigraphy in the follow-up of breast cancer. *Int J Biol Markers* 1997; 12: 154–157.