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# Lack of correlation between Tc-99m-sestaMIBI uptake and cadherin expression in infiltrating ductal breast carcinoma as prognostic indicators

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Despite using various kinds of prognostic indicators, it is still not possible to predict the biological behavior of breast cancer in all patients. Tc-99m-sestaMIBI (MIBI) uptake determined by breast scintigraphy and cadherin expression of tumor tissue revealed by immunohistochemistry are suggested as potential agents for this purpose. We hypothesize that there can be a correlation between MIBI whose cellular mitochondrial content is claimed to play a significant role in its tumor uptake and cadherin whose downregulation causes an increase in mitochondrial activity in human mammary carcinoma cell lines. The aim of this study was to assess the relationship between the degree of MIBI tumor uptake and cadherin expression in infiltrating ductal breast carcinoma. Correlation with response to chemotherapy and some known prognostic factors of breast cancer such as tumor size, number of metastatic axillary lymph nodes and microscopic grading was also done. Fourteen patients who underwent scintimammography and subsequent surgical excisional biopsy that revealed infiltrating ductal carcinoma were enrolled in this study. Statistical analysis did not show any correlation between MIBI uptake and cadherin expression ($p > 0.05$). Also, no statistically significant correlation was noted between MIBI uptake and tumor size, number of metastatic lymph nodes, microscopic grade, stage of the disease or response to chemotherapy. Similarly, there was no statistically significant correlation between cadherin expression and tumor size, number of metastatic lymph nodes, microscopic grade, stage of the disease or chemotherapy response. The results of this study imply that there is no correlation between MIBI tumor uptake and cadherin expression with neither of them good enough to be used as prognostic indicators for breast cancer.

**Key words:** breast cancer, prognosis, technetium-99m-MIBI, scintimammography, cadherin

## INTRODUCTION

Infiltrating ductal carcinoma (IDC) is the largest group of female breast cancer, constituting 70% of the total with a five year relative survival rate of 79%.[1] Prediction of prognosis has a great importance for the management of primary breast cancer. Routine axillary lymph node dissection is currently the standard of care in the staging, determination of prognosis and treatment protocol of breast carcinoma. The most useful and consistent of the prognostic factors for breast cancer is the presence and number of positive axillary lymph nodes.[2] Although this method has significant implications on the determination of prognosis and treatment protocol, it does not change patient survival and complications such as upper

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extremity lymphedema can be anticipated in 5–8% of breast cancer patients undergoing this operation.[3] Despite using various kinds of prognostic factors, it is not possible to predict the biologic behavior of 25–35% of all breast tumors.[4] Therefore, additional prognostic indicators are needed to determine appropriate treatment and predict prognosis. Recently, breast scintigraphy using Tc-99m sestaMIBI (MIBI) and cadherin expression of tumor tissue revealed by immunohistochemistry are suggested as potential agents for this purpose. Although, the mechanism of increased uptake of MIBI in breast tumors is not understood entirely, there is strong evidence that cellular mitochondrial content plays a significant role in its tumor uptake with it being concentrated up to 1,000 times into mitochondria in a dose-dependent fashion.[5] MIBI has also been validated as a transport substrate for p-glycoprotein and MRP1 in cultured multidrug resistant (MDR) rodent and human cell lines.[6,7] Recently, it was also shown that functional downregulation of cadherin on tumor cells regulates mitochondrial activity in human mammary carcinoma cell lines.[8] Although it has not thus far been studied at length, more aggressive tumors seem to have higher uptake of MIBI and cadherin negative IDC display higher histological grade and more lymph node metastases.[9,10] However, there are also controversial reports about the utility of these factors, and their value as independent prognostic indicators remains to be established.[11,12] The purpose of this retrospective study was to assess the relationship between the degree of MIBI tumor uptake and cadherin expression in invasive breast cancer. Correlations with some known prognostic factors of breast cancer and response to chemotherapy were also investigated.

## MATERIALS AND METHODS

*Patient selection*

Among patients who underwent prone scintimammography (SMG) and subsequent surgical excisional biopsy, those revealing infiltrating ductal carcinoma were enrolled in this study. All patients had axillary dissection as part of the standard clinical staging. For the purpose of this study, the histologic slides of these patients were requested from the pathology archives. Cases were excluded if the histologic slides could not be located or if the quantity or quality of the remaining paraffin-embedded tissue was insufficient for further study.

*Tc-99m MIBI scintimammography*

SMG was performed using a gamma camera equipped with a low energy, high resolution collimator (ADAC Genesys, CA, USA; GE Starcam, GE Medical Systems, Milwaukee, WI, USA). Each patient received an intravenous injection of 740 MBq of MIBI in the arm contralateral to the breast with the abnormality. Prone lateral imaging of each breast was performed for 10 minutes at 5–10 min postinjection with a 10% window centered at 140 keV, by using 256 × 256 matrix size and 1.33 zoom factor. The anterior view was obtained with the patient supine and both arms held above the head. Any focal area of increased uptake was considered as positive for malignancy in each study. Semiquantitative analysis of MIBI breast images was done by drawing region of interests (ROI) around the hottest area in tumor (T) and an area of normal breast tissue in the same breast encompassing the most homogeneous area of breast tissue (BG). Number of counts per pixel in each region was calculated. Results were expressed as a tumor-to-background (T/BG) ratio.

**Table 1** Data of 14 patients with infiltrating ductal breast carcinoma

| Patient no. | T/BG | Tumor size (cm) | Pancadherin expression (composite score) | Microscopic grading | Stage of the disease | Chemotherapy response |
|---|---|---|---|---|---|---|
| 1 | 3.98 | 3.5 | 7 | 2 | T3N1M0 | NR |
| 2 | 3.8 | 5 | 7 | 2 | T2N1M0 | CR |
| 3 | 3.1 | 5 | 0 | 2 | T2N1M0 | CR |
| 4 | 4.07 | 4 | 4 | 1 | T3N1M0 | PR |
| 5 | 1.57 | 5.5 | 7 | 2 | T3N2M0 | PR |
| 6 | 3.1 | 7 | 5 | 2 | T3N1M0 | PR |
| 7 | 1.85 | 5 | 5 | 1 | T2N2M0 | NR |
| 8 | 1.62 | 4.5 | 7 | 1 | T2N2M0 | PR |
| 9 | 1.15 | 2.5 | 7 | 2 | T2N2M0 | CR |
| 10 | 2.35 | 5 | 9 | 2 | T2N2M0 | CR |
| 11 | 1.47 | 10 | 6 | 2 | T4N1M0 | NR |
| 12 | 1.46 | 3.5 | 3 | 1 | T2N1M0 | NR |
| 13 | 1.45 | 2.5 | 4 | 2 | T2N1M0 | CR |
| 14 | 1.4 | 2.5 | 9 | 2 | T2N1M0 | CR |

NR: No response; PR: Partial response; CR: Complete response

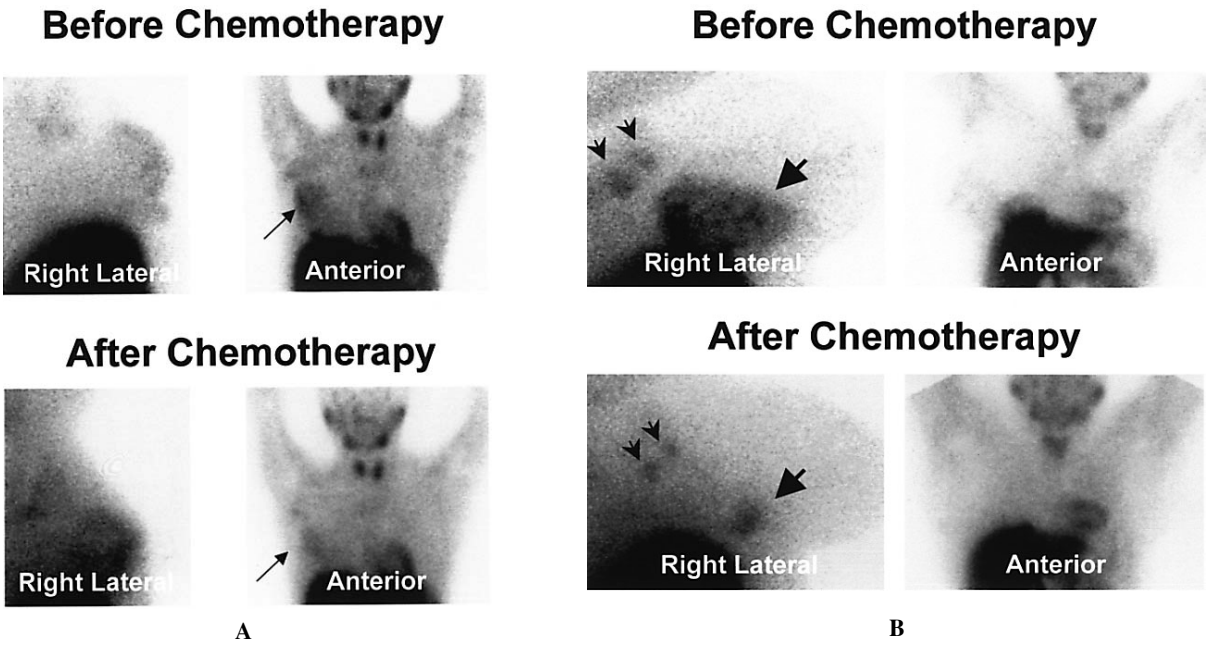


**Fig. 1** Tc-99m-MIBI scintimammography images of a 37-yr-old woman with 10 cm mass in her right breast (patient no. 11) (A). Surgical biopsy confirmed infiltrating ductal carcinoma. T/BG ratio before chemotherapy is 1.47 and MIBI uptake increased (T/BG: 2.24) after chemotherapy with no decrease in tumor mass (*arrows*). Tc-99m-MIBI scintimammography images of a 49-yr-old woman with 7 cm mass in her right breast and lymph node involvement (patient no. 6) (B). Surgical biopsy confirmed infiltrating ductal carcinoma. T/BG ratio before chemotherapy is 3.1 and MIBI uptake decreased (T/BG: 2.1) after chemotherapy with significant decrease in tumor mass (*arrows*).

*Chemotherapy protocol and definition of response status*

As chemotherapy, 4 courses of TEF regimen was given (80 mg/m$^2$ Docetaxel (taxotere), 70 mg/m$^2$ Epirubisin (epidoksorubisin) and 500 mg/m$^2$ 5-fluorourasil). Investigations for response evaluations included: Physical examination, x-ray mammography and MIBI scintimammography for the evaluation of local recurrence and tumor size measurement; x-ray computed tomography and Tc-99m-MDP bone scan for the evaluation of distant metastasis. Definition of complete response was the complete disappearance of all tumor lesions. Partial response was defined as a >50% decline in the product of the 2 greatest perpendicular tumor dimensions but not complete disappearance.[13] Patients not achieving a 50% decline in the product of maximal tumor dimensions or having new lesions or distant metastasis were considered to be nonresponders.

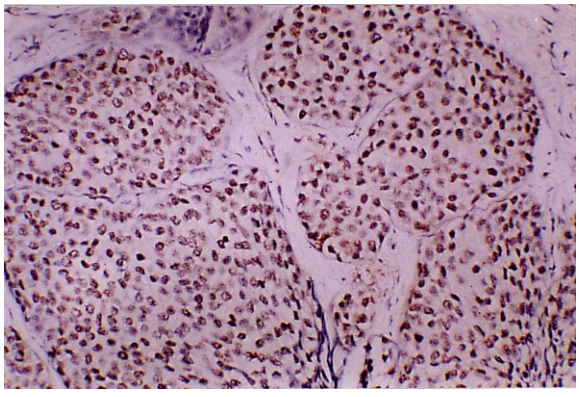

**Fig. 2** Pancadherin expression of a patient with a composite score of 9 (patient no. 10). T/BG ratio is 2.35. She has axillary lymph node involvement and a complete response to chemotherapy. Immunoperoxidase, background hematoxylin, × 200.

*Histologic immunostaining and immunostaining interpretation*

Tissues were fixed in 10% neutral buffered formalin, dehydrated and embedded in paraffin. 5 micrometer thick sections were cut by a sliding microtome. After deparaffinization, they were rehydrated. Protease digestion for antigen retrieval lasted 10 minutes. Endogenous peroxidase activity was blocked by 0.3% $H_2O_2$-methanol solution. Indirect immunoperoxidase method was used for immune staining. Incubation with primary antibody (anti-pancadherin monoclonal antibody, Sigma cat. no. C1821, Sigma, St. Louis, MO) lasted an hour. Primary antibody was omitted in negative control tissue sections. Phosphate buffered saline at pH 7.4 was used as washing solution. Incubation with secondary antibody (anti-mouse IgG peroxidase conjugate, Sigma cat. no. A9044) lasted half an hour. After washing, sections were processed in chromogen (3,3′ diaminobenzidine tetrahydrochloride,

**Table 2** Non-parametric analysis between MIBI uptake, pancadherin expression and some prognostic factors of breast cancer

| | Correlation coefficient | Probability |
|---|---|---|
| T/BG and pancadherin expression | –0.155 | 0.598 |
| T/BG and tumor size | 0.393 | 0.165 |
| T/BG and microscopic grading | –0.118 | 0.688 |
| T/BG and stage of the disease | 0.222 | 0.445 |
| T/BG and chemotherapy response | –0.176 | 0.547 |
| T/BG and number of metastatic lymph node | 0.294 | 0.308 |
| Pancadherin expression and tumor size | –0.064 | 0.827 |
| Pancadherin expression and microscopic grading | 0.362 | 0.203 |
| Pancadherin expression and stage of the disease | 0.285 | 0.324 |
| Pancadherin expression and chemotherapy response | 0.262 | 0.365 |
| Pancadherin expression and number of metastatic lymph node | –0.403 | 0.153 |

97%, Sigma cat. no. D5637) solution for 15 minutes. Hematoxylin was used for background staining. Sections were investigated under light microscope semiquantitatively by two histologists working separately. Staining intensity was scored from 0 (staining intensity equivalent to background staining) to 5. For each specimen section, 5 areas of interest at 40 times magnification were evaluated and their mean value of intensity was recorded. The percentage of stained cells was scored from 0 to 4 according to Gamallo et al.[10] Less than 5% stained cells were considered as 0, 5 to 25% cells as 1, 26 to 50% cells as 2, 51 to 75% cells as 3 and 76 to 100% cells as 4. For each specimen section, 5 areas of interest at 40 times magnification were evaluated and their mean values were recorded. Also, any variance between the recordings of the two histologists was overcome by taking the average value into account. A composite score was determined by adding the intensity and percentage scores.

*Microscopic grading*

Microscopic grade was obtained by adding up the scores for tubule formation, nuclear pleomorphism and mitotic count which were translated into the final grade.[14]

*Statistical analysis*

Statistical analysis was performed using independent sample t-test, Wilcoxon's Matched-Pairs Signed-Ranks test and Mann-Whitney-U test. Spearman and Pearson correlation tests were used to determine the relationships of semiquantitative data. Results were considered statistically significant when p values <0.05. Data were presented as median (mean, range). All calculations were performed using SPSS for Windows, version 6.0.

## RESULTS

Patients' clinical stage, tumor size, microscopic grade and response to chemotherapy are presented in Table 1 together with scintigraphic data and pancadherin expression. Statistical analysis did not show any correlation between T/BG and pancadherin expression ($p > 0.05$). Also no statistically significant correlation exists between T/BG and microscopic grade, number of metastatic lymph nodes, stage of the disease or response to chemotherapy (Fig. 1). Non-parametric analysis provided a low positive correlation between T/BG and tumor size, which was not statistically significant ($r = 0.393$, $p = 0.165$). There was no statistically significant correlation between pancadherin expression and tumor size, microscopic grade, number of metastatic lymph nodes, stage of the disease or response to chemotherapy (Fig. 2). Data of non-parametric analysis of T/BG and pancadherin expression are presented in Table 2.

## DISCUSSION

Predicting the metastatic potential and disease outcome is becoming increasingly important in breast cancer for planning treatment strategies. Currently the most important conventional independent prognostic factors, considering both patient's survival and early recurrence, are the presence and number of involved axillary lymph nodes and tumor size given by TNM staging. Additionally, microscopic grading is also found useful for prediction of prognosis. Generally the recurrence rate increases with greater tumor size and axillary node involvement, and these patients need more aggressive treatment. Recently, scintigraphic determination of cellular MIBI uptake and cadherin expression are suggested as additional prognostic factors to determine the biological aggressiveness of IDC and a valuable tool for predicting chemotherapy response.[9,10,15,16]

In addition to myocardial perfusion studies MIBI is also widely used for the differential diagnosis of breast masses. Biochemical and cellular pharmacological studies have suggested that MIBI, which is a lipophilic cation, is passively transferred across the cell membrane and concentrated in the mitochondria in response to transmem-

brane potentials.[17] Cellular uptake depends on the uptake by mitochondrial inner matrix and thus may account for MIBI accumulation in tumors such as breast carcinoma. Besides the proven mechanism (mitochondrial retention) several studies have investigated the other features that may affect tumor uptake of MIBI[18,19] MIBI is also a substrate for the multidrug resistance related p-glycoprotein efflux pump, with cells with high p-glycoprotein expression having markedly reduced MIBI uptake both in cell cultures and *in-vivo* studies with breast cancer patients.[7,20,21] However, none of these mechanisms is good enough to explain MIBI tumor uptake and alternative mechanisms are still waiting to be determined.[19] Recently, Bracke and co-workers have shown that functional downregulation of e-cadherin/catenin complex leads to increased mitochondrial activity in human mammary carcinoma cell lines.[8] As both MIBI and cadherin are claimed to be potential prognostic indicators in invasive breast cancer, and evidence exists that functional downregulation of cadherin on tumor cells regulates mitochondrial activity in human mammary carcinoma cell lines, we hypothesize that there might be a relation between uptake of MIBI in tumor and cellular expression of cadherin. Cadherins are a family of calcium-dependent, cell adhesion molecules whose reduced or lack of expression has been associated with tumor dedifferentiation and increased metastatic potential in human carcinomas.[22] A correlation has also been reported between cadherin expression and axillary node involvement in breast cancer.[23] However, different groups reported discordant results. Oka and colleagues found that reduced E-cadherin expression was associated with axillary node involvement, whereas Lipponen and co-workers could not confirm this.[22,24,25] Sitonen and co-workers showed that loss of normal E-cadherin expression is an indicator of increased invasiveness and dedifferentiation in breast carcinoma.[23] They concluded that E-cadherin is a potentially important prognostic factor in IDC. Charpin and colleagues found that reduced E-cadherin expression is an independent indicator of poor survival in node negative patients.[26] In short, the role of cadherin expression in clinical breast cancer remains unclear.[27] Although the established role of cadherins is mostly in cell to cell adhesion, they are also involved in inhibiting nuclear signaling by binding with beta catenin which is a proto-oncogene. So cadherins can be expressed in the cell nucleus as well indicating its link to DNA and cell growth. E-cadherin is shown to inhibit the growth of a colorectal tumor cell line named SW480.[28] All E-cadherin constructs posessing a beta catenin binding region displayed this growth inhibitory activity whereas constructs having only adhesive activity did not. Gottardi and co-workers suggested that loss of E-cadherin expression upregulates the beta catenin nuclear signaling pathway in human cancers.[28] Beta catenin affects the transcriptional activity in the nucleus and is directly related to tumorigenesis.[28] Also VE-cadherin is found to regulate signaling through VEGF receptor[29] and reported to inhibit cell growth.[30] Whereas P-cadherin expression is demonstrated to be an indicator of poor prognosis in infiltrating ductal breast carcinoma.[10] So different types of cadherins are involved in tumorigenesis but their relation to cell growth differs greatly and is not yet clear for any of them. Cytoplasmic domain of cadherins which lack adhesive function is shown to promote adenoma to carcinoma transition in a pancreatic tumor model.[31] As a consequence, cytoplasmic domain of cadherins must be the domain involved in cancer. Because of these facts we have used a monoclonal anti-pancadherin antibody which is obtained against a highly conserved sequence from the cytoplasmic C-terminal of N-cadherin. This terminal is the part interacting with catenins. Mitochondrial membrane depolarization reduces the net uptake of MIBI whereas hyperpolarization increases it.[32,17] It is very interesting that cadherin/catenin complex is functionally related to mitochondrial activation[8] and so to mitochondrial membrane depolarization as a prerequisite for activation. It is suggested that beta catenin is involved in the signal transduction towards the mitochondria.[8] It seems logical to suggest a relation between cadherin/catenin complex and mitochondrion which carries DNA like the nucleus. There should not necessarily be a direct functional relation between cadherin/catenin complex and mitochondrial MIBI uptake but we hypothesized that this complex may promote the uptake of this agent by causing hyperpolarization of the mitochondrial membrane. Contrary to our hypothesis, according to results of our study no correlation was found between MIBI uptake and pancadherin expression. Also, there was no statistically significant correlation between pancadherin expression and tumor size, microscopic grade, number of metastatic lymph nodes, stage of the disease or response to chemotherapy.

In our patient group, the average lesion size was 4.67 cm with a minimum of 2.5 cm and maximum of 10 cm. We found a positive low correlation between T/BG and tumor size, which was statistically not significant. Controversial results about MIBI uptake and lesion size also exist in the literature.[9,11,33] We also could not find a correlation between MIBI uptake and TNM status of the patients and number of involved axillary lymph nodes. Our study indicates that MIBI uptake can not be used as a prognostic indicator for breast cancer. Arslan et al. and Scopinoro et al. could not find any relationship between the number of involved lymph nodes and MIBI uptake either.[11,18] However, Cwikla et al. found that more aggressive tumors have higher uptake of MIBI.[9] Also, according to the results of our study, MIBI uptake can not predict the response to chemotherapy. However, we could not study p-glycoprotein expression and multidrug resistance in these patients which may affect MIBI uptake and response to chemotherapy.[34] In this study we used a single static pre-treatment MIBI scintigraphy to predict progno-

sis and chemotherapy response. A double phase scintigraphy with an early 10–15 min image and a late 60–120 min image which provides tumor washout of MIBI is also recommended for this purpose.[15,35] In the literature both single phase and double phase MIBI scintigraphies are used with similar success for this purpose.[16,36]

In conclusion we could not find any correlation between MIBI tumor uptake and pancadherin expression. Moreover, our study reveals that neither MIBI tumor uptake nor cadherin expression is good enough to be used as prognostic indicators for IDC.

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