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Can MIBI be a prognostic indicator?

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ABSTRACT

Introduction: *The study presents the correlation analysis between ^{99m}Tc-sestaMIBI uptake and the histological grade, most important prognostic factor of breast cancer.*

Material and method: *41 female patients of palpable breast masses with established breast carcinomas were entered into the prospective study. All the patients underwent planar ^{99m}Tc-sestaMIBI Scintimammography. The images were processed with ROI processing protocol and Lesion to Normal values (LNR) were obtained. Nottingham modification of Bloom and Richardson method was used for the histological grade of the tumour.*

Outcome: *A positive correlation (r = 0.31, p = 0.04) was found between sestamibi uptake and the histological grade of the breast carcinoma.*

Conclusion: *^{99m}Tc-sestaMIBI can prove to be a valuable prognostic indicator for invasive breast cancer prior to surgery. It will be helpful in influencing physician's decision regarding initiation of adjuvant therapies in high risk patients.*

Key words: ^{99m}Tc-MIBI, breast carcinoma, scintimammography, malignancy grade

INTRODUCTION

Breast cancer mortality has decreased significantly during the previous decades because of early detection due to advancement in imaging techniques and the early use of adjuvant systemic therapy. The purpose of adjuvant therapy is to eradicate distant micro-metastatic deposits. Therefore, it is of utmost importance to estimate an individual patient's risk of bearing clinically silent micro-metastatic disease using established prognostic factors. Prognostic factors are helpful in stratifying patients into two main groups such as those who can benefit from adjuvant therapy and those in which the risks out weigh the benefits of adjuvant therapy. A prognostic factor is any measurement available at the time of surgery that predicts disease free survival in the absence of adjuvant systemic therapy and is in turn able to correlate with the natural history of the disease (1). These factors are capable of giving useful information to the clinician at the time of diagnosis about the disease outcome and its indicators of growth, invasion and metastatic potential independent of therapy. Histopathological tumour grade is an important and well established prognostic factor. The grade of breast cancer is an important indicator of aggressiveness and overall prognosis. The 10 year survival in grade I tumours is around 85% where as the survival rate falls to 45% for grade III tumours.

The goal of the study is to correlate the semi- quantitative MIBI uptake analysis with

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histological tumour grade in breast nodules. Such correlation of MIBI uptake with histo-pathological analysis before surgery could facilitate selection of patients who are at high risk and need adjuvant therapy. ❑

MATERIAL AND METHOD

During 2006-2008 a total of 41 female patients with proven histo-pathological breast carcinoma were referred to the nuclear medicine and diagnostic imaging centre for mammography, ultrasonography and ^{99m}Tc-MIBI scintimammography. The prospective study was conducted with patients having the following inclusion criteria:

- Patients with palpable breast masses and diagnosed breast carcinoma.
- Not received prior radiotherapy or chemotherapy.
- Patients gave informed consent.

The detailed history of the patient was taken regarding the epidemiological and risk factors of breast cancer. All the data was collected and entered into the designed forms. Patients with palpable masses were evaluated clinically followed by X ray mammography (Mx), Ultrasonography (US) and Scintimammography (SM). The clinical size of the tumour was estimated with US using a high frequency (7.5 MHz) linear transducer. The maximum dimension of the tumour was recorded. ❑

Planar scintimammography technique

Scintimammography was done within 2-3 days of mammographic imaging. The functional breast imaging was done using rectangular shaped dual head gamma camera (Signature series e-cam, Siemens) equipped with a high resolution, low energy collimator. The energy was centered on 140kev ± 10% window. Lateral ans anterior images were acquired on 256x256 matrix. The head of the camera was adjusted so that skin of the breast was almost touching the collimator. An average dose of 950 MBq of methoxy isobutyl iso-nitrile (MIBI) was administrated (ranging between 740-1110 MBq). The dose was calculated according to the body weight of the individual as 11.1 MBq/Kg (0.3 mCi/Kg). Pre and post injection syringe radioactivity was estimated to calculate the exact dose. I.V. injection was given in the fore-arm vein contra-lateral to the site of lesion, followed by 5 ml saline flush. Within 5-10 minutes of injection the acquisition was started. Each patient was positioned prone on a Scintimammography bed placed on gamma camera patient bed with breasts freely pendant but separated by lead separation shield between two breasts. The patient bed was positioned between the two heads of the gamma camera. The height of the bed was adjusted to keep breast in the center of field of view extending from the neck to the upper level of the abdomen in order to visualise the breast and the ipsilateral axilla. The position was made comfortable by allowing the head rotation to one side and arms raised above the head. Lateral breast planar or static views were acquired simultaneously for 10 minutes with a zoom factor of 1.3. Similarly, an anterior static view was also acquired for 5 minutes after the lateral acquisition when the patient was in supine position. Semi-quantitative Scintimammographic interpretation was done. The lateral images of scintimammogram were displayed in ROI processing programme of the gamma camera for quantitative analysis. The images were displayed in coloured format available in the display programme. A coloured vertical bar with varying colours corresponding to the level of activity was shown along the image ranging from highest (on the top) to the lowest (on the bottom). The tumour was identified and a region of interest (ROI) was drawn on the point of maximum intensity within the lesion corresponding to the highest level of counts in the region. Similar sized ROI was also drawn on the opposite breast. Both background corrected Lesion and Normal ROIs were generated to calculate LNR (Lesion to Normal Ratios).

Histological grade

Nottingham modification of Bloom and Richardson method was utilized for histological grading of tumours as it is reproducible and correlates well with the survival. In this method tubule formation, nuclear pleomorphism and mitotic frequency are evaluated and scored accordingly. The tumors are graded from 1 to 3. Higher is the differentiation, lower is the score and grade of the tumour and better is the prognosis. Similarly with least differentiation, higher is the tumour grade with association of worse prognosis.

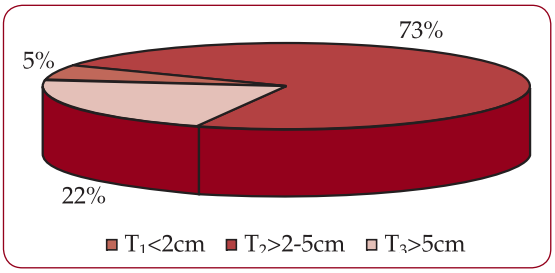
Statistical analysis

The Histological grades of the tumor were correlated with LNR values using correlative coefficient. The statistical significance was also estimated using 95% confidence interval. ❑

RESULTS

The mean age of the patients at the time of presentation was 46 ±12 ranging from 25 to 70 years. It was found that 61% (25/41) patients had tumours in their left breast. Remaining 39% (16/41) patients had tumours in the right breast.

Mean size of the tumour was 4.3 cm ± 2.3 range (1.8-12.0 cm). The largest size of the tumour was 12.0 cm with the smallest being 1.8 cm. The breast tumours size was grouped into 3 categories (T_1 ,T_2,T_3). The majority of masses i.e. 73% (30/41) were inT_2 size range (>2.0 to 5.0 cm). The next highest category of 22% (9/41) was T_3 with size larger than 5 cm. There were only 5% tumours (2/41) in group T_1 that had size less than 2 cm.



GRAPH 1. Percentage of tumours in clinical size categories

From 41 malignant palpable breast masses, 93% (38/41) were found to be infiltrating ductal carcinoma (IDC), 5% (2/41) mixed infiltrating ductal & lobular and 2% (1/41) in-situ ductal carcinoma.

Histopathological grading of 41 malignant tumours showed that 44% (18/41) had histological

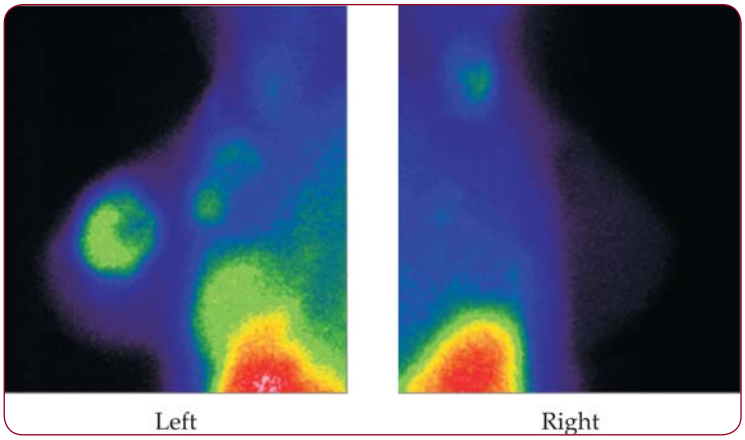


FIGURE 1. Patient No. 5.
Patient presented with infiltrating ductal carcinoma (3.1 cm in maximum dimension) in left breast. The mass showed intense radiotracer uptake and lesion to normal value (LNR) as 13.27 in histological grade III.

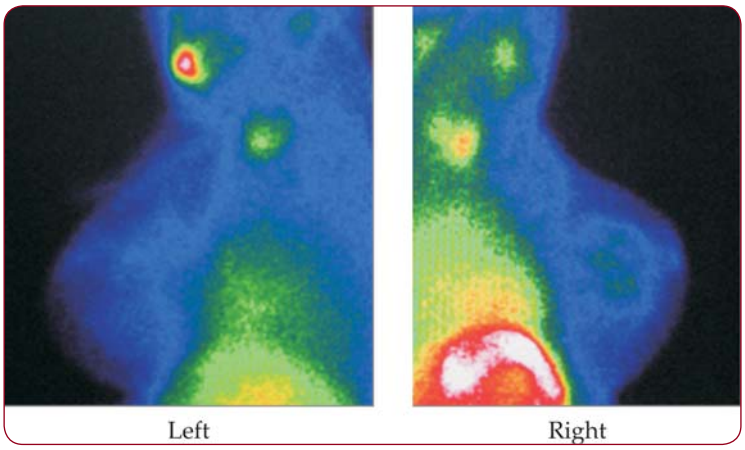


FIGURE 2. Patient No. 24.
Patient presented with infiltrating ductal carcinoma & infiltrating lobular carcinoma (4.0 cm in maximum dimension) in right breast. The mass showed moderate radiotracer uptake and lesion to normal value (LNR) as 2.54 in histological grade II

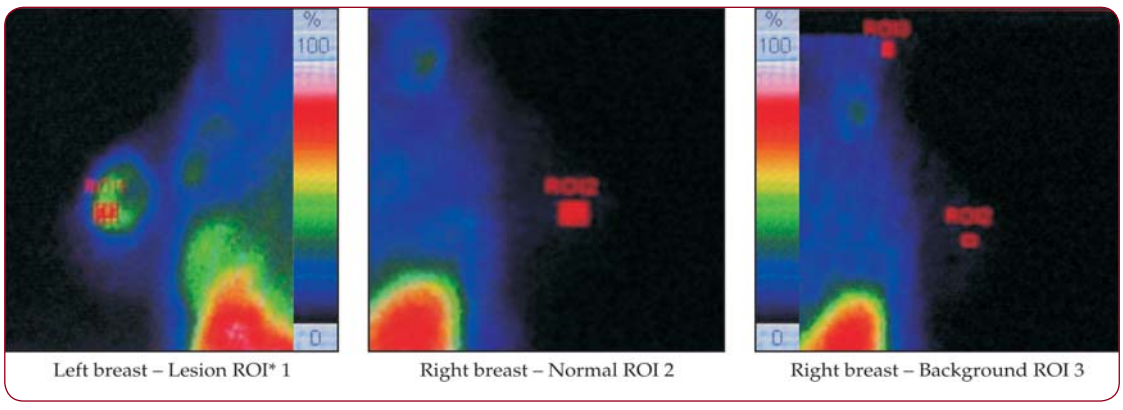
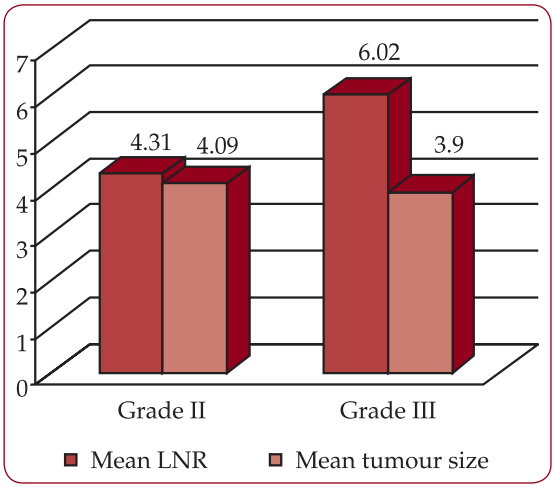


FIGURE 3. Region of interest for semi-quantitative analysis
*Region of interest

grade II and 56% (23/41) had higher grade i.e III. The average LNR value for grade II tumours were 4.3 ± 1.8 ranging from 2.2. to 8.4 and for grade III tumours were 6.0 ± 3.5 varying from 2.5 to13.8.



GRAPH 2. Graphical comparison in histological grade II & III of mean LNR value & tumour size

Positive correlation (r = 0.31, p = 0.04) was found between LNR and grade of the tumours. Clinical tumour size was also correlated with LNR value. Slight correlation (r=0.25, p = 0.05) was found between these two variables. ❑

Parameter	Correlation Co-efficient	p-value
1. Histological grade	0.31	0.04
2. Tumour size	0.25	0.05

LNR Correlation with various parameters

DISCUSSION

Disease progression depends on various factors such as clinical and histo-pathological features of the tumor (e.g. TNM staging and histo-pathological grade). Histopathological grade and is assumed to be the most important prognostic factor and relate to the survival of the patient. A good prognosis in breast malignancy is associated with small tumour size, low histopathological grade and absence of metastasis. On the other hand, large tumour size, high malignancy grade and presence of metastasis are associated with poor prognosis and decreased survival of the patient. Early detection of these prognostic factors along with the diagnosis of breast cancer can identify the risk to each patient. Such identifications can guide the treating physician to initiate adjuvant therapy or make aggressive approach in the management of these cases.

New radiological modalities and ^{99m}Tc-sestaMIBI is under evaluation for the assessment and analysis of prognostic factors. A study by Cwikla et al (2) indicated that uptake of MIBI can be evaluated for in vivo tumour behaviour and showed that radiotracer uptake in primary breast cancer positively correlated with tumour size, axillary lymph node involvement and tumour grade. In the present study, tumour uptake is quantified as background corrected lesion to normal values and correlated individually with the most significant prognostic factors such as tumour size and histological grade. The point of maximum activity within the tumour was selected to rule out the accompanying inflammatory or necrotic component of the mass. It is a well known fact that gamma camera is unable to detect tumours less than 1 cm; but in the present study all the sizes of the cancers were more than 1 cm. Therefore the limitations of the camera were not exercised and the tumours were detected quite easily.

In this study, a positive correlation is observed among LNR and grades of the tumour. Grade II tumours have lower LNR values with an average of 4.3 as compared to 6.0 of grade III tumours. Higher the grade of the tumour more intense was the uptake of MIBI while in patients with low-grade disease the MIBI uptake was comparatively low. High grade indicates greater un-differentiation of the malignant tissue, related with high mitotic activity in the rapidly dividing cells. The un-differentiated cancer cells grow rapidly, metabolism increases, RNA and protein synthesis is elevated, and organelles duplicate (i.e. mitochondria doubles in number). Increased uptake is dependent upon the higher mitotic activity of the tumour, as MIBI is concentrated maximally within the mitochondria (i.e. 90%). Many earlier studies have shown that MIBI concentrates within the mitochondria owing to lipophilic character and electrostatic forces. In tissues with high cellular division the mitochondrial population would be high. Several investigators have found a positive correlation between MIBI uptake and mitotic index, cellular atypia and higher nuclear grade of the tumour (3). This would suggest that more aggressive tumours have higher uptake of ^{99m}Tc-MIBI (4). The negative plasma membrane potentials accumulate the lipophilic cation in the cytoplasm relative to the extra cellular spaces and strongly negative mitochondrial

membrane potentials should further concentrate MIBI within the inner mitochondrial matrix relative to cytoplasm, the net concentration in the mitochondria (5,6). The results of this study are partly in agreement to what the other studies had shown.

It has been proposed that morphological aspects of higher tumour grade may contribute essential information both for the prospective outcome of the individual patient and for TNM staging. It appears that ^{99m}Tc-MIBI uptake during early pre-operative evaluation could provide valuable information about tumour biological characteristics and thereby influencing therapeutic planning.

Tumour size and LNR values are slightly correlated with $r = 0.25$. In the study population, certain breast cancers with large size did not show intense radiotracer accumulation and small sized tumours had intense radiotracer uptake. The larger size masses as they grow rapidly their center become necrotic leading to less radiotracer uptake while the small sized cancers contain more viable dividing tissue resulting in greater accumulation. The uptake of MIBI within the tumours is also affected by many factors. Various other clinical studies have correlated the MIBI uptake with different cellular processes such as apoptosis, proliferation, P-gp expression and neo-angiogenesis. Apoptosis is an energy dependent, highly regulated process leading to selective cell death. When mitochondria receives death signal, it causes an early increase in the permeability of mitochondrial membrane and release of cytochrome-c and other apoptogenic factors that trigger the downstream sequence of reactions (7). The mitochondrial membrane permeabilisation is regulated by the opposing actions of pro- and anti-apoptogenic Bcl-2 family members (8). Bcl-2 is an integral protein of the outer mitochondrial membrane and exerts a strong inhibitory effect on the permeabilisation of mitochondrial membrane, the opening of the mitochondrial permeability transition pore and the disruption of mitochondrial membrane potentials. ^{99m}Tc-MIBI uptake is related to apoptosis because it is reversibly accumulated within the mitochondria and its influx is dependent on mitochondrial membrane potentials. Breast carcinoma which fails to accumulate MIBI has an altered apoptotic process due to over expression of anti-apoptotic protein Bcl-2 (9). The expression of anti-apoptotic protein is also inversely correlated with the early tumour to background ratio in MIBI positive malignant lesions. Not only reduced inward movement of radiotracer is responsible for low accumulation but rapid extrusion is also another reason. Since MIBI is also a transport substrate of P-glycoprotein and over expression of P-gp is responsible for reduced tracer uptake in the tumour cells. It represents a powerful mechanism of MIBI extrusion from the cells (10-11). ❑

CONCLUSION

Results advocate that Scinti-mammography is a non-invasive risk-free and easily performed procedure. Nuclear medicine imaging is not only capable of imaging primary lesions, but is also suitable for characterization of tumor and providing useful information on biological features that will assist in estimating the prognostic indicators earlier during the process of diagnosis. This is of utmost importance as it will be beneficial to high risk individual and initiating adjuvant therapy early in the course of disease.

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