

Original Article

ROLE OF SCINTIMAMMOGRAPHY IN LOCALLY ADVANCED BREAST CANCER (LABC)

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ABSTRACT

Neo-adjuvant chemotherapy is used in cases of locally advanced breast cancer (LABC) aiming for local control of the disease and cosmetic breast surgery.

The aim of the work: is to assess the response of LABC to neo-adjuvant chemotherapy by Tc-99m MIBI & Tc-99m (V)DMSA scintimammography in relation to histopathological evaluation.

Materials & Method: 24 patients with locally advanced breast carcinoma, aged 30 to 65 years were included. Initial scintimammography using Tc-99m MIBI& Tc-99m (V) DMSA was done using 20 mCi of each tracer. Early images at 20 minutes as well as late images at (2 hours in case of Tc-99m MIBI & 4 hours in case of Tc-99m(V)DMSA) were acquired. After 3-4 courses of neo-adjuvant chemotherapy, scintimammography was repeated using both tracers. All the images were assessed qualitatively according to grade of uptake & quantitatively by drawing region of interest over the breast lesion and a mirror image over the contra-lateral normal breast. L/N ratio was calculated for each image. The degree of change in Tc-99m MIBI & Tc-99m (V)DMSA uptake from pre-therapy scan to post-therapy scan was calculated. Correlation between the degree of change of Tc-99m MIBI & Tc-99m(V)DMSA and histopathological percentage of necrosis, antibody expression for angiogenesis& MDR were done.

Results: *Good response* was evident in 9 patients, 88.8% of them showed significant degree of change in Tc-99mMIBI uptake ratio, while only 33.4% showed partial degree of change in Tc-99m(V)DMSA uptake ratio. The percentage of change in Tc-99mMIBI uptake in this group ranged from 43% to 58% with mean value of 51.6%, while that of Tc-99m(V)DMSA ranged from -9.2% to 18% with mean value of -2.4%. *Partial response* was evident in 5 patients. All of them showed partial degree of change in Tc-99mMIBI uptake while Tc-99m(V)DMSA uptake showed no change in all the five patients. The degree of change of Tc-99mMIBI ranged from 4 %to 46% with mean value of 19.7%, while that of Tc-99m(V)DMSA ranged from -5.5% to -19.9% with mean value of -12.4%. *Bad response:* 10 patients showed bad response. All the ten patients showed no change in Tc-99mMIBI uptake ratio, while 50% showed no changed in Tc-99m(V)DMSA uptake ratio. The percentage of degree of change in Tc-99mMIBI ranged from-12% to 17% with mean of 2.59, while that of Tc-99m(V)DMSA ranged from -25 to 5.2 with mean value of -6.7

There was highly statistically significant correlation between degree of change of Tc-99m MIBI & percentage of histopathologic necrosis, angiogenesis as well as antibody expression against MDR (P < 0.01), whereas no significant correlation was found between degree of change of Tc-99m(V)DMSA &

percentage of necrosis, angiogenesis and expression of MDR ($P > 0.05$).

Key words: *Scintimammography, locally advanced breast cancer, Tc-99m MIBI, Tc-99m(V) DMSA*

INTRODUCTION

Breast cancer is the most common malignant tumor among women that account for 32% of their cancer and is considered one of the leading causes of death in women in USA (*Raymond et al., 1995*).

Breast cancer is treated by a combination of surgery, chemotherapy & radiotherapy. The use of neo-adjuvant chemotherapy as the first line of treatment followed by external beam radiotherapy, and Conservative breast surgery is the standard protocol for locally advanced breast cancer (*Touboul et al., 1996*).

Assessment of response of primary breast cancer to neo-adjuvant chemotherapy is an important issue in the treatment protocol. This is done by clinical evaluation and radiological procedures using mammography & ultrasound, however the anatomical imaging can not evaluate residual viable tumor tissue accurately.

^{99m}Tc Sestamibi is a radio-pharmaceutical used in cardiac imaging and as a tumor imaging agent. ^{99m}Tc Sestamibi Scintimammography has sensitivity of 92.2% and specificity of 89.2 % in detection of breast carcinoma. Scintimammography plays an important role in assessment of tumor response to neo-adjuvant chemotherapy in breast cancer. This is accomplished by determining the extent of viable tumor versus fibrosis or necrosis through comparing base line and post therapy scans using both qualitative and

quantitative measures (*Khalkhali et al., 2000*).

Another important issue in treatment with chemotherapy is evaluation of multidrug resistance (MDR) which is considered as a stand point for further modification of treatment protocol. A good correlation between the expression of Pgp (P-glycoprotein) responsible for multidrug resistance and rate of efflux of Tc-99m sestamibi (*Del Vecchio et al., 1997*), hence ^{99m}Tc sestamibi can be used in evaluation of multidrug resistance (MDR).

^{99m}Tc (V) Dimercaptosuccinic acid (DMSA) is a tumor imaging agent that has been used to image various tumors. Studies reported it's usefulness in scintigraphy of medullary cancer thyroid and breast carcinoma (*Papantoniou et al., 2001*).

Objectives

- To compare the reliability of ^{99m}Tc sestamibi & ^{99m}Tc (V)DMSA in assessment of response of locally advanced cancer breast to neo-adjuvant chemotherapy.
- To determine role of radionuclide as in-vivo imaging of multi-drug resistance.
- Comparison of radionuclide imaging with pathological data including MDR, percentage of necrosis and angiogenesis.

PATIENTS AND METHODS

24 female patients with breast carcinoma were included in our study. Their age ranged from 30 years to 65 years old with mean age of 48.14 years. Local axillary examination showed that 15 patients have palpable enlarged firm fixed lymph nodes, while 14 patients' exhibits no axillary node involvement.

Initial pre-chemotherapy Scintimammography using ^{99m}Tc sestamibi and ^{99m}Tc (V)DMSA was done. A dose of 20 mCi of ^{99m}Tc - sestamibi & ^{99m}Tc (V) DMSA was injected I.V. Early images were acquired at 20 minutes post injection. Planar Views for the breast were acquired both in anterior and lateral position for the affected breast and the contralateral one for a total count of 1000 K count. Whole body scanning was acquired following the early planar views to determine the possibility of distant metastasis. Late Images were acquired after 2 hours from injection in case of using ^{99m}Tc sestamibi and 4 hours in case of using ^{99m}Tc (V)DMSA. Planar views for both breasts were acquired in the same position as in the early images and for the same time acquired in the early image. Region of interest was drawn on the site of lesion with mirror image of the region of interest drawn on the contra lateral normal breast for calculation of lesion to normal ratio(L:N) in the early and late images for ^{99m}Tc sestamibi and ^{99m}Tc (V)DMSA.

All the twenty four patients received 3-4 courses of neo-adjuvant chemotherapy. They were evaluated clinically and radiological by CT chest, abdominal sonography, as well as ^{99m}Tc MDP bone scan. 20 patients had done modified radical mastectomy and 4 patients underwent conservative surgery.

Post chemotherapy Scintimammography using ^{99m}Tc sestamibi & ^{99m}Tc (V)DMSA was done and assessment of response was estimated qualitatively and quantitatively. **Qualitative assessment was done by** comparing the grade of uptake before and after neo-adjuvant chemotherapy protocol and determine the degree of change in the grade of uptake (no change, Partial change and Significant change). **Quantitative assessment:** L/N ratio was compared before and after neo-adjuvant chemotherapy protocol. The degree of change was calculated by subtracting L/N ratio of the post-therapy scan from that of

the pre-therapy scan divided by the pre-therapy scan L/N ratio.

Patients were divided into 3 groups: good, partial and bad responders. *Good responders* are those who showed significant decrease in grade of uptake with decreased L/N ratio < 1.5 . *Partial responders* are those who showed partial decrease in grade of uptake and L:N ratio but still > 1.5 . *Bad responders* showed no change or higher grade of uptake with L/N ratio > 1.5 .

Histopathological examination of all the surgical specimens was done to determine the effect of Neo-adjuvant chemotherapy and percentage of necrosis as well as Immunohistochemical staining to detect MDR and angiogenesis. The degree of angiogenesis was classified into mild (+), moderate (++) and significant (+++).

All the results of scintimammography & pathological data were compared and analyzed according to standard statistical methods.

RESULTS

A- ^{99m}Tc MIBI scintimammography:

Good responders: Nine patients (37.5%) out of the twenty four patients showed good response to chemotherapy by histopathological examination. Eight patients (88.88%) out of the nine patients showed significant change in the grade of uptake of Tc-99m MIBI from the initial pre-chemotherapy scan to post chemotherapy scan. There was concordance between the degree of change in the grade of MIBI uptake and the response to chemotherapy, such result was statistically highly significant ($r = 0.87$). (Fig 1) **Quantitatively** the percentage of degree of change in the MIBI uptake from the initial pre-chemotherapy scan to the post chemotherapy scan ranged from 43 % to 58 % with mean value of 51.6% (Table 1), (Fig. 2A).

Table (1): Quantitative assessment of response to chemotherapy using ^{99m}Tc MIBI scintimammography.

	Pre-chemotherapy mean uptake ratio	Post-chemotherapy mean uptake ratio	Degree of change in MIBI uptake	
			Range	Mean
Good responders:				
• Early	2.17 ± 0.44	1.06 ± 0.13	43 – 58 %	51.6%
• Late	2.04 ± 0.35	0.97 ± 0.28		
Partial responders:				
• Early	2.31 ± 0.83	1.78 ± 0.21	4 – 46 %	19.78%
• Late	2.18 ± 0.81	1.63 ± 0.17		
Bad responders:				
• Early	2.24 ± 0.86	2.34 ± 0.96	-12 – 17 %	2.59%
• Late	2.20 ± 0.88	2.14 ± 0.83		

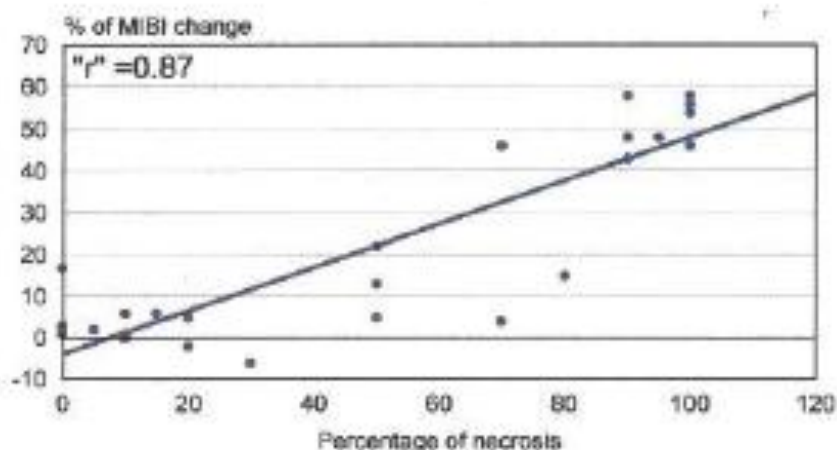


Fig. (1): Correlation between degree of Tc-99m MIBI change and percentage of histopathologic necrosis

Histopathological examination of the surgical specimens revealed that the percentage of necrosis in all nine patients who showed good response was more

than 90% necrosis (*Fig. 2B*) these cases showed mild degree of angiosasis and where MDR negative (*Fig. 2C, D*).

Table (2): Quantitative assessment of response to chemotherapy using ^{99m}Tc(V)DMSA.

	Pre-chemotherapy mean uptake ratio	Post chemotherapy mean uptake ratio	Degree of change in ^{99m} Tc-(V)DMSA	
			Range	Mean
Good responders:				
• Early	2.08 ± 1.02	2.05 ± 0.88		
• Late	1.95 ± 1.03	1.94 ± 0.85	-9.2 to 18%	2.4%
Partial responders:				
• Early	2.5 ± 0.52	2.7 ± 0.67		
• Late	2.2 ± 0.59	2.5 ± 0.75	-5.5% to -19.9%	- 12.4%
Bad responders:				
• Early	1.88 ± 0.96	1.78 ± 0.75		
• Late	1.7 ± 0.22	1.6 ± 0.71	-25 to 5.2%	- 6.7%

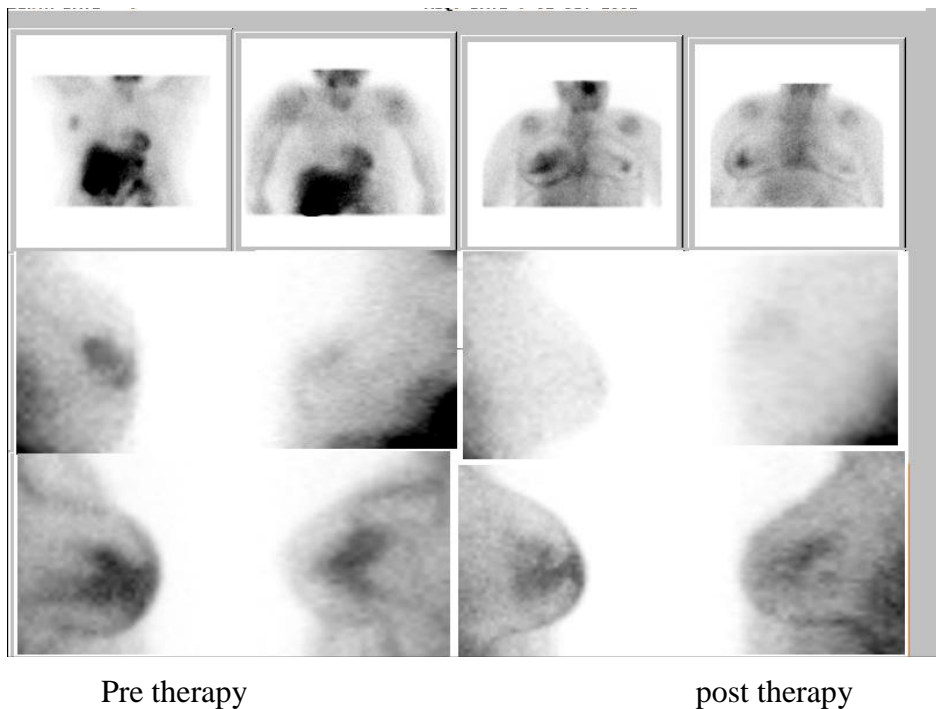


Fig. (2A): Tc-99m MIBI & Tc-99m (V)DMSA Scintimammography showing significant degree of change in Tc-99m MIBI uptake while mild change is noticed in (V) DMSA scintimammography.

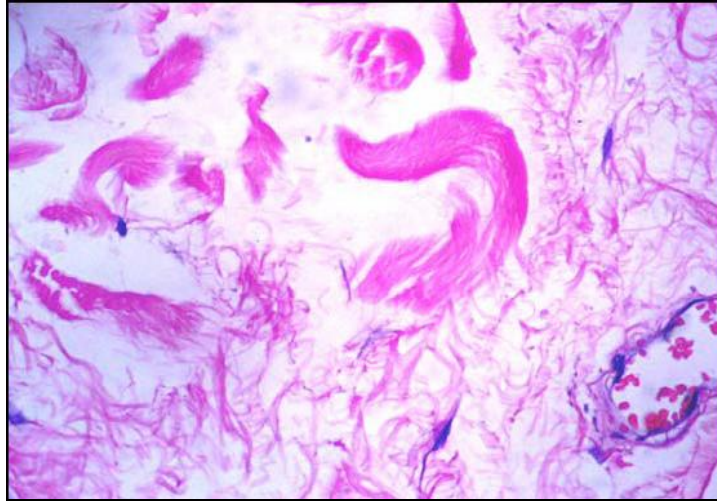


Fig. (2B): Histopathological examination showing percentage of necrosis > 95%.

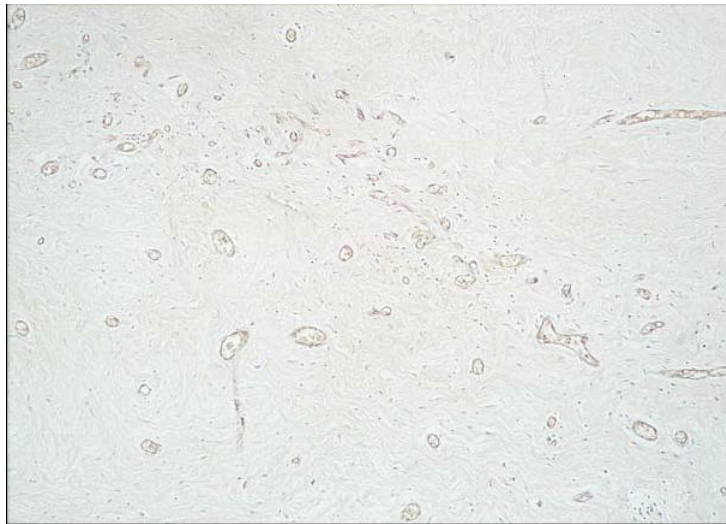


Fig. (2C): Immunohistochemical staining using F-8 for angiogenesis and showed mild degree of angiogenesis.

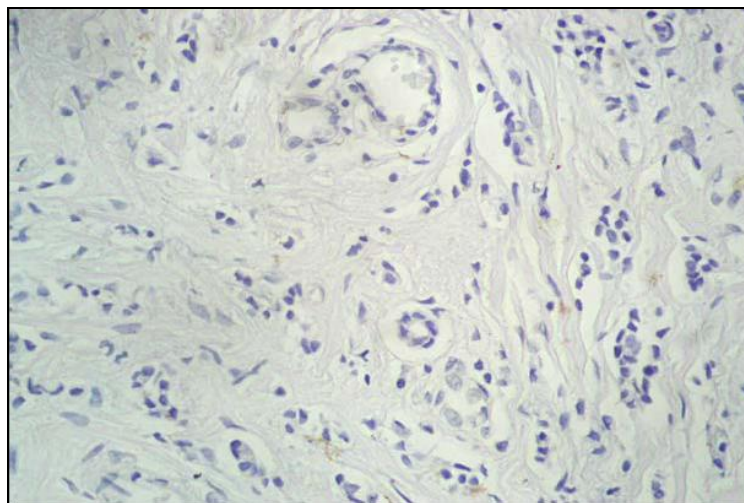


Fig. (2D): Immunohistochemical staining using P-170 for MDR-1 and showed negative staining.

Partial Responders Five patients out of the twenty four patients showed partial response to neo-adjuvant chemotherapy by histopathological examination. All the five patients showed partial change in the grade of MIBI uptake from the initial pre-chemotherapy scan to the post chemotherapy scan. **Quantitatively** The patients of this group showed decrease in MIBI uptake ratio from the initial pre-chemotherapy scan to the post chemotherapy scan but still the mean value of post chemotherapy MIBI uptake is more the normal value (1.5).. The percentage of change in the MIBI uptake from the initial pre-chemotherapy scan to the post chemotherapy scan ranged from 4% to 46% with mean value of 19.78% (Table 1).

Histopathological examination of the surgical specimens revealed that the percentage of necrosis ranged from 50%-90%

Bad responders Ten patients out of the 24 patients showed bad response to neo-adjuvant chemotherapy. All the ten patients showed no change in the grade of MIBI uptake from the initial pre-chemotherapy scan to the post chemotherapy scan. **Quantitatively** The percentage of change in MIBI uptake from the initial pre-chemotherapy scan to the post-chemotherapy scan ranged from -12% to 17% with mean value of 2.59%. (Table 1) (Fig. 3A). Histopathological examination of surgical specimens of the ten patients who showed bad response revealed that the percentage of necrosis of this group of patients was < 50% (Fig.3B).these case showed high degree of angiogenesis and 3 of them were positive for MDR (Fig. 3C&D).

Correlation between percentages of change in: percentage of necrosis

Correlation between degree of change of ^{99m}Tc -MIBI from the pre-chemotherapy scan to the post chemotherapy scan and percentage of necrosis in the studied groups (good, partial & bad responders) were done. It

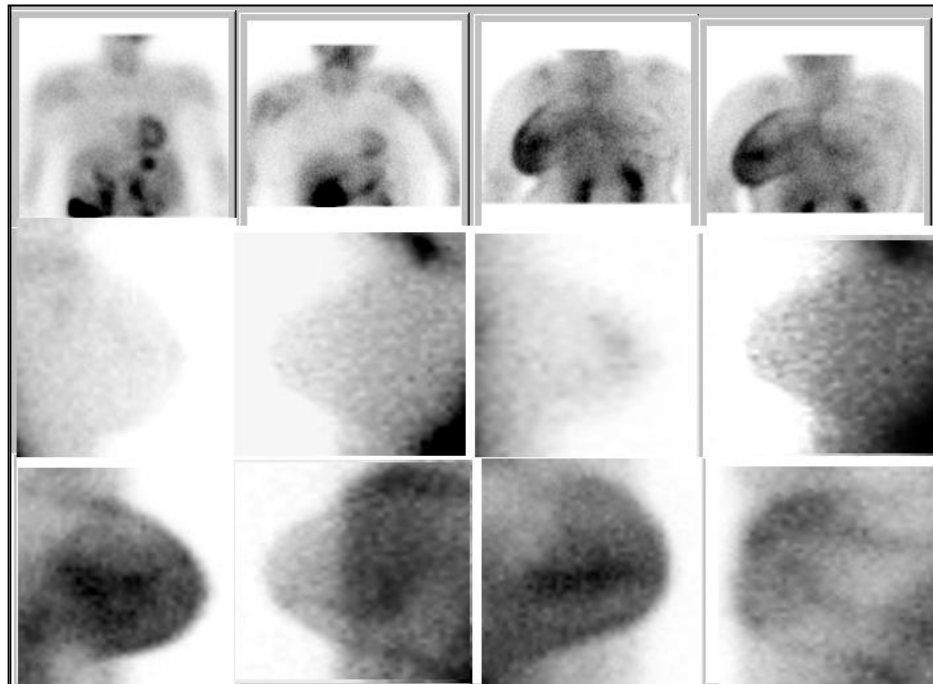
showed highly significant correlation with $r = 0.87$, p value < 0.01 (Fig.1).

B- ^{99m}Tc (V)DMSA scintimammography:

Good responders: Six patients of nine good responders (66.66%) showed no change in the degree of uptake from the initial ^{99m}Tc (V)DMSA pre-chemotherapy scan to the post chemotherapy scan. The other three patients (33.34%) showed partial degree of change. The degree of change in the grade of (V)DMSA uptake from the initial pre-chemotherapy scan to the post-chemotherapy scan in relation to response was statistically not significant ($P > 0.05$). **Quantitatively**, The percentage of the degree of change in ^{99m}Tc (V)DMSA from the initial pre-chemotherapy scan to the post- chemotherapy scan ranged from - 9.2% to 18% with mean value of 2.4% (Table 2) (Fig. 2A).

Partial responders All the five patients of partial response showed initial high grade of (V)DMSA uptake in the pre-chemotherapy scan with no change in the grade of uptake from the initial pre-chemotherapy scan to the post chemotherapy scan. **Quantitatively** the percentage of the degree of change in ^{99m}Tc (V)DMSA from the initial pre-chemotherapy scan to the post chemotherapy scan ranged from -5.59% to -19% with mean value of - 12.4% (table 2)

Bad responders Five out of the ten patients with poor response showed no change in the grade of Tc-^{99m} (V)DMSA uptake from the pre-therapy scan to the post-chemotherapy scan. The other five patients (50%) showed partial degree of change in the grade of (V)DMSA uptak. **Quantitatively** The percentage of the degree of change in ^{99m}Tc (V)DMSA from the initial pre-chemotherapy scan to the post chemotherapy scan ranged from - 25 to 5.2% with mean value of - 6.7% (Table 2) (Fig. 3A)). No correction was found between percentage of Tc (v) DMSA change with percentage of necrosis, angiogenesis or MDR expression.



Pre therapy

post therapy

Fig. (3A): Tc-99m MIBI & Tc-99m (V)DMSA Scintimammography showing no initial uptake in Tc-99m MIBI predicting the presence of MDR-1 as well as in post therapy scan, while almost the same grade of uptake of (V)DMSA is seen in the pre & post therapy scans in the Rt. Breast lesion.

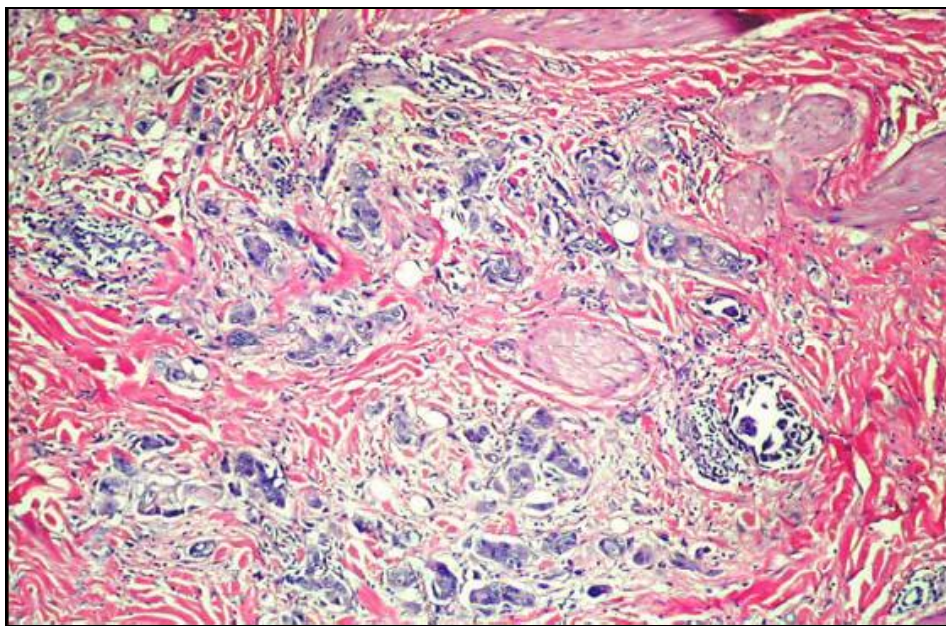


Fig. (3B): Histopathological examination showing no response to chemotherapy with 5% percentage of necrosis.

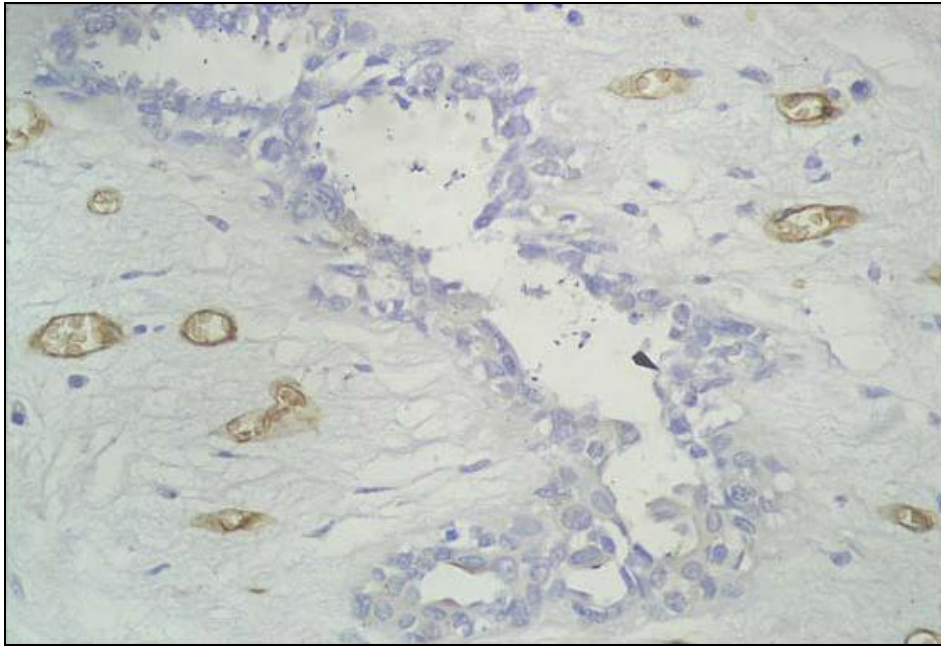


Fig. (3C): Immunohistochemical staining using F-8 for angiogenesis and showed moderate grade of angiogenesis.

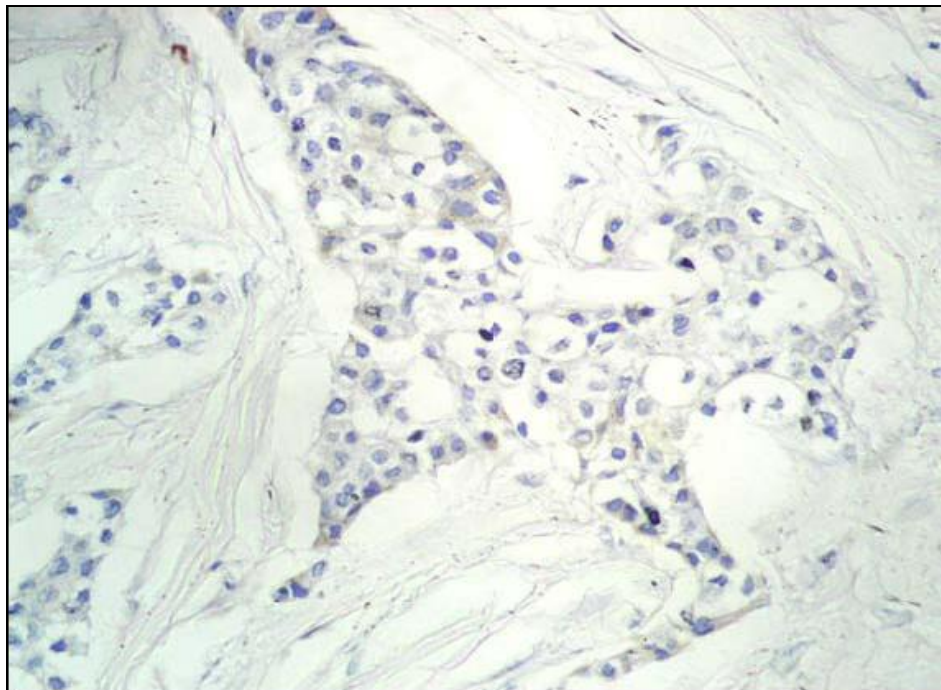


Fig. (3D): Immunohistochemical staining using P-170 for MDR-1 and showed positive staining.

DISCUSSION

The present study included 24 patients to assess response to neo-adjuvant chemotherapy using ^{99m}Tc -MIBI & ^{99m}Tc -(V)DMSA scintimammography. They are classified according to pathological response & percentage of necrosis into good, partial Tc-MRBI& bad responders.

Nine patients showed good response with percentage of necrosis > 90%. Eight patients of them (88.8%) showed significant change in grade of MIBI uptake that ranged from 43% to 58% with mean value of change of ^{99m}Tc -MIBI 51.6%. Five patients showed partial response with mean value of change in grade of MIBI uptake 19.8%. Ten patients showed percentage of necrosis < 50%. with mean value of change 2.59%. So, if the degree of change in ^{99m}Tc -MIBI uptake is higher than 43% this could predict good response to neoadjuvant chemotherapy in 89% of the patients.

Similarly, *Mankoff et al., (1999)*, investigated 32 patients with locally advanced breast cancer (LABC) with MIBI scintimammography prior to, after 2 courses and at completion of chemotherapy. They concluded that, the change in L/N ratio was 58% in complete pathological responders & 18% in partial pathological responders ($P < 0.005$). They also specify a change of $\geq 40\%$ in the MIBI uptake ratio could identify complete responders with 100% sensitivity and 89% specificity.

Also, *Takamura et al., (2001)* studied 46 patients with LABC or metastatic breast cancer and found that L/N ratio of MIBI uptake before therapy could predict response to chemotherapy with a PPV, NPV and accuracy of 81%, 96% and 89.1% respectively.

Furthermore, *Sciuto et al., (2002)* assessed 30 patients with locally advanced breast cancer by MIBI scintimammography at baseline and after the completion of neo-adjuvant

chemotherapy. They stated that with a pretreatment washout rate cut off at 45% the scan yielded a sensitivity of 100% and specificity of 80% for prediction of chemo-resistance. Positive and negative predictive values were 83% and 100% respectively.

Tc-99m (V) DMSA:

Six patients (66.6%) out of the nine patients with percentage of necrosis > 90% who proved to be good responders showed no change in degree of (V)DMSA uptake ratio, while only three patients (33.34%) showed mild degree of change in (V)DMSA uptake ratio from the pre-therapy scan to the post therapy scan with mean value of change of 2.4%.

Five patients showed partial response. They showed no change in the degree of (V)DMSA uptake ratio with mean change value of change -12.4%. Five patients in the group of bad response showed no change in degree of (V)DMSA uptake ratio, while the other five patients (50%) showed partial degree of change in the degree of (V)DMSA uptake ratio with mean value of change -6.7%. So, there was no definite correlation between degree of change in ^{99m}Tc (V) DMSA uptake and histopathological changes.

Angiogenesis:

In the present study, the degree of change of MIBI uptake from the pre-therapy scan to the post-therapy scan showed statistically highly significant correlation with angiogenesis (P value < 0.01), while the degree of change of (V) DMSA uptake from the pre-therapy scan to the post therapy scan showed no significant correlation with angiogenesis (P value > 0.05).

Also, *Bekis et al., (2005)* studied 31 breast lesion with ^{99m}Tc -MIBI scintimammography and immunohistochemical staining in attempt to correlate between the MIBI uptake and angiogenesis in breast lesions. They

found that there was no statistically significant correlation between the degree of angiogenesis and early L/N ratio ($r = 0.235$, $P > 0.05$), and delayed L/N ratio ($r = 0.18$, $P > 0.05$). On the other hand, they reported that there was high correlation between angiogenesis and washout index ($r = 0.893$, $P < 0.05$) in non invasive breast lesions.

Multi-drug Resistance:

Another important issue in treatment with chemotherapy is evaluation of multidrug resistance (MDR) which is considered as a stand point for further modification of treatment protocol.

A good correlation was found between the expression of Pgp (P-glycoprotein) responsible for multidrug resistance and rate of efflux of Tc-99m sestamibi (*Del vecchio et al., 1997*), hence Tc-99m sestamibi can be used in evaluation of multidrug resistance (MDR).

In the present study, all the surgical specimens included in the study were subjected to immunohistochemical staining for detection of P-gp expression in relation to the late uptake of both 99mTc-MIBI and Tc-99m(V) DMSA in the initial pre-therapy scan. MIBI scintimammography predicted the phenomenon of MDR with sensitivity of 75% & specificity of 95%. The relation between MDR-1 protein expression (P-glycoprotein) and late Pre-therapy MIBI uptake ratio was statistically significant with $P < 0.01$.

Also, *Cayre et al., (2002)* investigated 45 patients with invasive breast cancer using a single pre-treatment MIBI scan. Expression of MDR-1 and MRP mRNA were also determined by PCR on fine needle aspiration. High MIBI uptake tended to predict chemoresistance with a specificity of 100%. MIBI uptake was inversely correlated with the expression of MDR 1 gene ($P < 0.005$).

Furthermore, *Zhang et al., (2004)*, investigated 30 patients with pathologically confirmed invasive ductal carcinoma by 99mTc-MIBI scintimammography & Immunohistochemical staining for P glycoprotein and resistance associated protein (MRP). They calculated the retention index for every case and deduced that there is high positive correlation between P-gp and retention index ($r = -0.88$, $P = 0.001$), but no significant correlation between resistance associated protein (MRP) and retention index ($r = -0.12$, $P = 0.512$).

On the other hand, in the current study ^{99m}Tc-(V) DMSA scintimammography proved to have no role in prediction of MDR-1. Also, no correlation between the MDR-1 protein expression and late pre-therapy 99mTc-(V) DMSA uptake ratio.

Also, *Denoyer et al., (2003)* reported from their study on in vitro cell lines derived from human breast carcinoma that ^{99m}Tc-(V) DMSA is not related to either P-gp and MDR-1 expression or glutathione (GSH) levels.

CONCLUSION

Tc-99m MIBI scintimammography is valuable in assessment of response of LABC to neo-adjuvant chemotherapy, while Tc-99m (V) DMSA plays no role in assessment of response to neo adjuvant chemotherapy. 99mTc-Sestamibi scintimammography is a valuable method in prediction of multi-drug resistance in locally advanced breast carcinoma, while Tc-99m (V) DMSA has no role in prediction of MDR.

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