

# Interrelationship between Skeletal and Visceral Metastases in Invasive Ductal Carcinoma of Breast- Observational Study at INMAS, Mitford, Dhaka

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## ABSTRACT

**Background:** Invasive Ductal Carcinoma (IDC) is the most common of all diagnosed breast cancers, and it frequently presents with metastatic spread to the bone as well as other viscera. Bone scintigraphy is the primary tool for detecting bone metastases, while different imaging modalities can be useful in detecting visceral metastases. The purpose of this study was to determine the relationship between skeletal and visceral metastases in female patients with IDC referred to INMAS, Mitford, for bone scintigraphy.

**Patients and Methods:** This observational study was conducted at the Institute of Nuclear Medicine and Allied Sciences (INMAS), Mitford, Dhaka, from July 2020 to July 2021. Bone scintigraphy was done with a Siemens dual-head gamma camera after an intravenous injection of 20 mCi of <sup>99m</sup>Tc-MDP. Both anterior and posterior views were obtained, with additional SPECT images when needed. Images were interpreted and analysed by Nuclear Medicine (NM) physicians of this institute. Data about visceral metastases were collected from patients' record files.

**Results:** The patients were divided into two groups based on the presence of visceral metastases. Group-A had 95 patients with no known metastases to the viscera, and in Group-B, there were 50 patients who had documented visceral metastases. The majority of the patients in the first group (53.7%) showed no bone metastasis, while a small portion (5.3%) revealed a solitary skeletal metastatic lesion and the rest (41.1%) presented with multiple skeletal metastases. Sixty-six percent of patients in Group B had solitary visceral metastases, with the remaining 34% having metastases to multiple viscera. All the patients in this group were affected at various levels by secondary skeletal deposits.

**Conclusion:** The findings of the study revealed that the presentation of visceral metastases was related to the extent and severity of bone metastases in patients with carcinoma of the breast.

**Keywords:** Bone scintigraphy, breast carcinoma, visceral metastases, bone metastases.

Bangladesh J. Nucl. Med. Vol. 25 No. 2 July 2022

Doi: <https://doi.org/10.3329/bjnm.v25i2.64648>

## INTRODUCTION

Breast carcinoma is a complex and very divergent type of malignant condition. Among all subtypes, invasive ductal carcinoma (IDC) is the most common, affecting up to 80% of diagnosed cases. Other categories include invasive lobular carcinoma (ILC), ductal carcinoma in situ (DCIS), medullary carcinoma, inflammatory, tubular, papillary, and mucinous breast cancer, mammary Paget's disease, and Phyllodes tumor (1).

Metastatic progression of the disease is an important landmark in any breast cancer, and the dominant site of metastasis is one of the crucial prognostic factors. Bone is the most frequent metastatic site for this malignancy, which may be found with or without visceral metastases. The best survival is reported in patients with bone-only metastases (2). The advanced stage along with visceral metastases indicates a relatively poor prognosis compared to skeletal metastases (3). Multiple studies have addressed the complex milieu of metastatic breast carcinoma and identified several clinico-pathological risk factors behind its variable propensity towards different organs. Some notable factors include age at initial diagnosis, primary tumor size, grade, nodal status, receptor expression, and hormone receptivity (4).

A few studies have found that IDC has a higher risk of visceral metastases than lobular subtypes (3).

Nonetheless, NM institutes receive frequent referrals for bone scintigraphy from IDC patients at various stages of their disease course, as it is an effective imaging modality for the detection and follow-up of bony metastases. The present study was designed to find out the interrelation between skeletal metastases and visceral metastases among such patients in the context of their demographic pattern and immunophenotypic character.

## PATIENTS AND METHODS

This observational study was conducted at INMAS, Mitford, Dhaka, between July 2020 and July 2021, and included diagnosed female breast cancer patients referred from various hospitals for a bone scan. All the patients were histopathologically confirmed to have invasive ductal carcinoma. Bone

scintigraphy was done with 20 mCi  $^{99m}\text{Tc}$ -labelled methylene diphosphonate ( $^{99m}\text{Tc}$ -MDP) using a Siemens dual-headed SPECT gamma camera. Data about visceral metastatic lesions, the histopathology report, and detail immunohistochemistry were collected from the patients' medical record file. The statistical analysis of all the data was done with SPSS version 22.

## RESULTS

There were 145 patients in total, all of whom were female and ranged in age from 23 to 76 years (mean  $52.6 \pm 9.9$  years). They were divided into two groups (A and B) on the basis of visceral metastases. Group-A included the patients with no visceral metastasis, and Group-B patients were those with visceral metastasis (Table 1).

**Table 1: Characteristics of study subjects of Group-A and Group-B**

	<b>Group A</b>	<b>Group B</b>
<b>No. of patients</b>	95	50
<b>Age (years)</b>	23 – 76, mean $53.1 \pm 10.2$	31 – 69, mean $52.1 \pm 9.6$
<b>Receptor status</b>	ER/PR+ = 48 (50.6%) ER/PR- = 17 (17.9%) ER+/PR- = 18 (18.9%) ER-/PR+ = 12 (12.7%)	ER/PR+ = 17 (34%) ER/PR- = 10 (20%) ER+/PR- = 14 (28%) ER-/PR+ = 09 (18%)
<b>Treatment status</b>	Pre-treatment = 5 (5%) NACT = 7 (7.3%) NACT + Surgery = 11 (11.5%) Only surgery = 9 (9.4%) Surgery + CT = 21 (22.1%) Surgery + CT/RT = 27 (28.4%) Surgery + CT/RT/HT = 13 (13.6%) Palliative therapy = 2 (2.1%)	Pre-treatment = 1 (2%) Only surgery = 5 (10%) Surgery + CT = 11 (22%) Surgery + CT/RT = 17 (34%) Surgery + CT/RT/HT = 6 (12%) Palliative therapy = 10 (20%)
<b>Symptoms</b>	Asymptomatic = 15 (15.7%) Chest pain = 3 (3.1%) Back pain = 12 (12.6%) Shortness of breath = 2 (2.1%) Nausea = 7 (7.3%) Weight loss = 20 (21%) Cough = 9 (9.4%) Fatigue = 23 (24.2%) Others = 4 (4.2%)	Asymptomatic = 1 (2%) Chest pain = 10 (20%) Back pain = 9 (18%) Shortness of breath = 6 (12%) Nausea = 3 (6%) Weight loss = 5 (10%) Cough = 7 (14%) Fatigue = 5 (10%) Others = 4 (8%)

ER- Estrogen receptor, PR- Progesterone receptor, NACT- Neo-adjuvant chemotherapy, CT- Chemotherapy, RT- Radiotherapy, HT- Hormone therapy

The average age was almost similar in both groups (Table 1). Immunohistochemically, most of the patients had positive hormone receptor status (ER/PR+) in group A (50.6%) and group B (34%), while negative estrogen receptor and positive progesterone receptor (ER-/PR+) were the least common hormone receptor statuses (12% in group A and 18% in group B). Treatment-wise, the majority of cases in both groups underwent surgery as well as chemotherapy and radiotherapy. The majority of the patients experienced symptoms of several distinct types including fatigue and tiredness, disturbed sleep, pain, dry mouth, distress, numbness tingling and sadness, whereas just a small number of them were asymptomatic.

**Table 2: Pattern of bone involvement in Group-A patients (without visceral metastases) detected in <sup>99m</sup>Tc-MDP bone scan (n= 95)**

Negative for Metastases	Bone Metastases		Total
	Solitary	Multiple	
50 (53.7%)	10 (5.3%)	35 (41.1%)	95(100%)

Around 54% of the patients of Group-A were free from both visceral and skeletal metastases (Table 2). Whereas, many of the IDC patients of Group-B had mild or absent symptoms of their visceral metastases (mostly lung, liver and pleura) but positive skeletal metastases. The most commonly encountered pattern in Group-B was patients with single visceral metastasis (54%) and multiple skeletal deposits (52%). Extensive skeletal involvement was found in all patients with metastatic spread to more than two viscera.

**Table 3: Pattern of bone involvement in bone scan study of Group-B patients (n=50) having known visceral metastases**

Visceral Mets	Bone Metastases			Total
	Solitary	Multiple	Extensive	
Liver/lung	4 (14.8%)	16(59.3%)	7(25.9%)	27 (54%)
Liver, lung	1(7.7%)	7(53.8%)	5(38.5%)	13 (26%)
Lung, pleura	0(0%)	3(60.0%)	2(40.0%)	5 (10%)
Liver, lung, brain ± pleura	0(0%)	0(0%)	5(100%)	5 (10%)
Total	5 (10%)	26 (52%)	19 (38%)	50 (100%)

**Table 4 showed that solitary hepatic metastasis was found in the highest number of patients in group B. For multiple visceral metastases, the lung and liver were most commonly affected together.**

Site of visceral Mets.	Number (percentage)	Immunohistochemistry
Liver	23 (46.0)	ER/PR+ = 11 (47%) ER/PR- = 3 (13%) ER+/PR- = 7 (30%) ER-/PR+ = 2 (8%)
Lung	13 (26.0)	ER/PR+ = 5 (38.5%) ER/PR- = 2 (15.4%) ER+/PR- = 3 (23%) ER-/PR+ = 3 (23%)
Lung & liver	4 (8.0)	ER/PR+ = 2 (50%) ER/PR- = 1 (25%) ER+/PR- = 1 (25%)
Lung & pleura	5 (10.0)	ER/PR+ = 2 (40%) ER/PR- = 1 (20%) ER+/PR- = 2 (40%)
Lung, liver, brain	4 (8.0)	ER/PR+ = 2 (50%) ER+/PR- = 2 (50%)
Lung, liver, brain, pleura	1 (2.0)	ER/PR+ = 1 (100%)

**DISCUSSION**

Tumor biology and patient characteristics both play intricate roles in the metastatic progression of a primary malignancy. Many studies have been done to grasp the depth of this intricacy and provide a better understanding of the process, as metastases are always an alarming development in the course of a disease. In this regard, breast carcinoma needs special concern, being the most common malignancy worldwide and having a staggering percentage of risk for developing metastasis (5).

Age is an important factor in the pathophysiology of metastatic breast cancer. Purushotham et al. conducted a study to determine the relationship between distant metastasis in breast cancer and patients’ age at diagnosis. The highest number of patients were found to be in the 50–59 year age group, which is similar to our study (4). A slight difference was observed with the findings of Lee et al. regarding age (6). In their work, the mean age of the study subjects was 47 years, with a range of 18 to 75 years. However, considering the immunohistochemical profile, most of their patients were ER/PR positive, which is in accordance with our finding (Table 1). On the

other hand, Purushotham et al. reported that in their patient pool, most of the cases with bone metastases were ER/PR positive, and the majority of cases with visceral metastases were ER positive and PR negative (4, 5).

It is widely accepted that bone is the commonest metastatic site for breast cancer (2, 6, 7, 8). This is also reflected in the current study, where 95 out of 145 patients (65.5%) presented with bone metastases with or without visceral involvement. Again, in different studies (7), bone-only metastases were found to be more common than visceral metastases, but in our case, the number of patients with only skeletal metastases was 45 (31%), which was less than the number of patients with visceral metastases (34.5%).

A study conducted by Savci-Heijink et al. found that the most frequent metastatic site was the bone (76.6%), followed by the liver (54.5%), and then the lung (31.4%) (9). This observation was also corroborated by Soni et al., who showed that the skeleton was the most common site of metastases (48%), followed by the liver (27%), lung (23%), brain (17%), and pleura (7%). These findings were nearly consistent with the current study. We reported the highest number of secondary lesions in bones (65.5%), followed by the liver (64%), lung (54%), pleura (12%), and brain (10%) (Table 4). Besides, Yamamura et al. documented that about 32% of their study subjects had both bone and visceral metastases (10). This was very similar to our study (34.5%).

Limitation of this study was that it was conducted retrospectively focusing on a relative short time span. Prospective studies with larger cohort and longer duration may provide better insight on metastatic disease pattern as well as survival outcome.

## CONCLUSION

Our findings show that the presence of visceral metastases is linked to the extent and severity of bone metastases in patients with carcinoma breast. Also, bone metastases in the region caudal to the lumbosacral junction provided a clue to predict visceral metastases.

We believe that this new information can be used to determine the kind, scope, and intensity of treatment for each patient and help to explore the complex biological pathways underlying such metastatic behavior.

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