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Clinical Significance of ^{99m}Tc-MDP Imaging & Molecular Biology in the Diagnosis of Bone Metastases

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ABSTRACT: *Breast cancer is a leading cause of cancer death among women. Skeletal metastases are clinically significant because of associated symptoms, complications such as pathological fractures and their profound significance for staging treatment and prognosis. Detection of bone metastatic lesions allows radiation therapy or surgical interventions to prevent pathological fractures from disabling the patients. High sensitivity of bone scanning in determining the presence and extent of metastatic disease makes extremely important tool in decision making. Bone scans demonstrate metastatic lesions much earlier than X-ray,C.T.,MRI. To help diagnose pathology of the skeletal system, patients are injected with radiopharmaceuticals composed of Technetium-^{99m} and a bone-seeking molecule such as analogs of calcium, hydroxyl groups or phosphates. In fact the most commonly used molecule is organic diphosphonate bound to Tc-^{99m}. These patients are then scanned by a gamma camera 2-4 hours later; typically, both anterior and posterior scans are taken.Purpose of study was to diagnose, staging and see the treatment response in breast cancer patients. ^{99m}Technetium methylene di-phosphonate (^{99m}Tc MDP) bone scintigraphy was performed for the detection of bone metastases in histopathologically proven patients of breast cancer. 53 patients of breast cancer were investigated with gamma camera. On visual analysis there was positive scan findings (bone metastases) in 19 patients (35.84 %) and negative scan findings (normal bone scan) in 34 patients (66.6%). ^{99m}Tc-MDP skeletal scintigraphy elucidates, non-invasively, tumour characteristics and may be indicative for prognosis and response to chemotherapy and hormonal treatment.*

KEYWORDS: *Gamma camera, Bone scan, Bone metastases, Breast cancer, ^{99m}Tc-MDP, Skeletal scintigraphy*

I. INTRODUCTION:

Clinical research and medical therapies arising from molecular biology and the use of molecular cell biology approaches in medicine is now called molecular medicine. Biological molecules are predominantly three-dimensional and structural, it must inquire into genesis and function.[1] Molecular biology also plays important role in understanding formations, actions, regulations of various parts of cells which can be used efficiently for targeting new drugs, diagnosis of disease and physiology of the Cell.Breast cancer is a leading cause of cancer death among women. Mammography testing have improved early detection and treatment of breast cancer, slowing their increase in incidence over the past decade and increasing the 5-year survival rate to 98% for breast cancer when detected at the earliest stages. However, the breast cancer survival rate drops dramatically to 83% for patients initially diagnosed with regional spread and to 26% for those with distant metastases.[2] Hypoxia is a major contributor to tumor metastasis, regulating secreted products that drive tumor-cell proliferation and spread. Hypoxia also contributes to resistance to radiation and chemotherapy in primary tumors. Solid tumors are particularly susceptible to hypoxia because they proliferate rapidly, outgrowing the malformed tumor vasculature, which is unable to meet the increasing metabolic demands of the expanding tumor. [3] The radionuclide bone scan is the cornerstone of skeletal nuclear medicine imaging. Bone scintigraphy is a highly sensitive method for demonstrating disease in bone, often permitting earlier diagnosis or demonstrating more lesions than are found by conventional radiological methods. Primary tumours of bone are relatively rare in adults whereas metastases to bone are very frequent (breast, prostate, lung, head and neck cancer, etc.). This being particularly true for certain primary tumors.Skeletal metastases are clinically significant because of associated symptoms, complications such as pathological fractures and their profound

significance for staging treatment and prognosis. [4] The mechanism behind uptake of the radiodiphosphate is chemisorption (which is adsorption of a molecule to a surface based on chemical bond formation) on the surface of hydroxyapatite crystals of the bone matrix. The determinants of increased uptake are increased skeletal metabolic activity (primarily the extent of osteoblastic activity), the most important factor and accounting for increased uptake at growth centres and centres of osteoblastic and other metabolic activity, increased blood flow which causes vascular dilatation and hyperemia.The skeleton is a preferred site for breast and prostate cancer metastasis. Within the skeleton, metastases present as two types of lesions: osteoblastic or osteolytic. These lesions result from an imbalance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption. Osteoblastic lesions are caused by an excess of osteoblast activity relative to resorption by osteoclasts, leading to abnormal bone formation. In breast cancer, osteolytic lesions are found in 80% of patients with stage IV metastatic disease. The most common skeletal complication of breast cancer is osteolytic bone metastasis. Bone metastases are present in 80% of patients with advanced disease and cause significant morbidity. They are most often osteolytic, but can be osteoblastic or mixed. Tumor cells, osteoblasts, osteoclasts and bone matrix are the four components of a vicious cycle necessary for the initiation and development of bone metastases. [5] The lesions are characterized by increased osteoclast activity and net bone destruction. Breast cancer bone lesions span a spectrum, in which the majority is osteolytic, but up to 15% are osteoblastic or mixed. Metastasis to bone occurs in the late stages of tumor progression and is a multistep process. Cancer cells first detach from the primary tumor and migrate locally to invade blood vessels. Once in the bloodstream, cancer cells are attracted to preferred sites of metastasis through site-specific interactions between tumor cells and cells in the target tissue. [6] Tumor cells that metastasize to the skeleton adhere to the endosteal surface and colonize bone.

Radionuclide imaging (RNI) concerned with providing diagnostic information about patients following the administration of a radioactive product. Images are produced of the distribution of the radioactive substance within different organs and systems. This can be compared with normal distribution to diagnose if a medical condition is present and assess its extent or severity.The skeletal is one of the most common sites of distant metastasis in many cancers. Bone scan or scintigraphy (BS) using ^{99m}Tc-methylenediphosphonate (MDP) is considered the most sensitive method of detecting skeletal metastases, and has been used routinely in higher-risk cancer patients, especially in breast, prostate, and lung cancers, which are known for their high incidence rate of bone metastasis. For the detection and evaluation of bone metastases of various kinds of carcinomas, ^{99m}Tc-bone scintigraphy has been used widely because of its overall high sensitivity and the easy evaluation of the entire skeleton. Breast Cancer is **most prone to metastasize to long bones.** Present scenario involves ^{99m}Technetium methylene di-phosphonate (99mTc MDP) bone scintigraphy method of choice for the detection of bone metastases.To help diagnose pathology of the skeletal system, patients are injected with radiopharmaceuticals composed of Technetium-^{99m} and a bone-seeking molecule such as analogs of calcium, hydroxyl groups or phosphates. In fact the most commonly used molecule is organic diphosphonate bound to Tc-^{99m}. These patients are then scanned by a gamma camera 2-4 hours later; typically, both anterior and posterior scans are taken. Aims of the study is to evaluate 99mTc-MDP is superior in detecting osseous metastasis than conventional bone scans & 99mTc-MDP scintigraphy detects unusual site of skeletal metastasis in patients of breast cancer.

II. METHOD:

This study has been performed at the division of Nuclear Medicine, Department of Radiation Oncology, Hamidia & Kamla Nehru Hospital, Gandhi Medical College, Bhopal, India. Sum of 53 females, 25-72 years were accounted for the study. Out of which 50 females was histopathologically diagnosed as cancer breast. They have been referred to nuclear medicine for bone scan and two patients came directly with the history of lump in breast with pain in joints. All patients underwent whole-body bone planar scintigraphy in the anterior and posterior positions 3 hours after injection before and, after surgery, radiotherapy, chemotherapy and during follow-up. A dose of 22 to 25 mCi 0f ^{99m}Tc-MDP was injected IV, entire skeleton was taken under the Electronics Corporation of India Limited (ECIL) gamma camera imaging machine equipped with a low-energy high-resolution parallel-hole collimator.All spot views were taken as the primary method of acquisition, the regions of the skeleton covered by each spot view. The first spot view of the axial skeleton, usually the posterior projection of the chest, was acquired for approximately 500,000 to 1 million counts depending on the field of view (FOV) of the gamma camera. The larger the FOV, the larger the number of total counts required to give similar count densities over equivalent regions of the skeleton. Moreover, the presence of physiologically high count density organs (typically the kidneys) may hamper visualization of contiguous structures (typically the spine). Each of the remaining spot views was then acquired for the same time as the first view. Spot images were obtained using a 128.128 or a 256×256 matrix (>200,000 counts).

Reporting: Nuclear medicine physician record appropriate information regarding the patient, especially type of examination, date, radiopharmaceutical (administered activity and route), a summary of patient history, all correlated data from previous diagnostic studies and the clinical problem. Findings, abnormal tracer uptake (increased, decreased, pattern of abnormal uptake, bone findings, soft tissue findings) were noted. We also wrote comparative data (correlation with other diagnostic results and comparison with previous studies in the reports. In Interpretation, a clear diagnosis is given.

III. RESULTS:

In this study, diagnosis of advanced breast cancer were also included, all patients underwent both a bone scan and other conventional imaging procedure, including plain film radiography n=50, computed tomography (n=6) for confirmation of metastatic disease. Follow-up data were retrieved from routine clinical evaluation by means of physical examination, imaging, biopsy reports and blood analysis. Our observations was that the 99mTc-MDP bone scan is very sensitive for localization of skeletal metastases or tumours, but the specificity is low.As per our patients data we found a total of 53 patients of breast cancer were investigated with ECIL gamma camera. On visual analysis there was positive scan findings (bone metastases) in 19 patients (35.84 %) and negative scan findings (normal bone scan) in 34 patients (66.6%). In four patients with available follow-up data two with a positive ^{99m}Tc-MDP scan remained stable and two of three patients with a negative 99mTc-MDP bone scan had progressive disease. Looking to the clinical significance of study, we recommend 99mTc-MDP bone scan is must before and after surgery, chemotherapy/radiotherapy and follow-up to increase the survival and quality of life of the patients suffering from deadly disease breast cancer. To determine the potential role of 99mTc-MDP bone scintigraphy for the evaluation of bone metastases helps in diagnosis and prediction of treatment response in breast cancer patients.

IV. DISCUSSIONS:

Over recent decades, bone scintigraphy has been used extensively in the evaluation of oncological patients. It provides essential information about the sites of bone lesions (primary and metastatic tumours), their prognosis and the effectiveness of therapy by showing the sequential changes in tracer uptake. ^{99m}Technetium methylene diphosphonate (99mTc MDP) bone scintigraphy is currently the method of choice for the detection of bone metastases, but 18F-fluoro-deoxy-D-glucose positron emission tomography (18FDG PET) offers superior spatial resolution and improved sensitivity. We have compared 18FDG PET with 99mTc MDP bone scintigraphy in patients with skeletal metastases from breast cancer and have analyzed the data in subgroups based on radiographic characteristics of lesions **[7]**.The standard diagnostic method since the 1970's is planar or SPECT scintigraphy using 99mTc labeled polyphosphonates. Studies by Schirrmeister et al. **[8]** demonstrated that planar bone scintigraphy was 80-90% sensitive in the detection of peripheral skeletal metastases, but as low as 20-40% sensitive in the detection of vertebral metastases. Evaluation of metastatic bone disease is possible using FDG PET. FDG accumulates in all cells relative to increased glucose metabolism. Soft tissue as well as bony metastatic sites can demonstrate FDG uptake, making precise anatomic localization of lesions difficult.^{18}F NaF is preferentially deposited at sites of high bone turnover and remodeling, and bone metastases are seen indirectly because uptake depends on skeletal reaction to the tumor. Tracer kinetics depend on both regional blood flow and osteoblastic activity with bone uptake two times higher and blood clearance is faster than 99mTc labeled polyphosphonates, resulting in superior bone to background ratio. In present study, we have observed the crystal clear and superior entire skeletal to background ratio (Fig: 4 & 5), by which we were accurately diagnosed all lesions of bone metastases in patients of breast cancer.

Radionuclide bone scanning using technetium-labeled polyphosphonates was introduced into clinical practice in the 1970s and was shown to detect BM several months earlier than plain radiographs. Therefore, BS has become one of the most frequently performed nuclear medicine procedures in Europe and the United States. However, the number of BS procedures used in oncology has been reduced because the prevalence of BM in patients with early tumor stages is low and early treatment of metastatic bone disease does not necessarily improve the survival rate. Furthermore, several studies that compared the sensitivity of planar BS with that of MRI have shown that planar BS is less sensitive than previously accepted. **[9]-[13]** This study observed high sensitivity but less specificity in osteolytic type of the lesions.The spine is a common site of bony metastasis. To date, studies have not identified the initial site and pattern of vertebral metastasis in a homogeneous group of patients. Although radiographically an absent pedicle is often the first sign of metastatic disease, involvement of the pedicle is by direct extension from either the vertebral body or the posterior elements and is therefore a late occurrence in the disease process. **[14]** Our research depicted vertebral bone metastatic lesions[Fig: 5] before it appear in radiography. The combination of functional and morphologic findings with PET/CT increases the diagnostic performance of PET alone. Since the first prototype PET/CT scanner was built in 1998 **[15]-[16]**, several studies have demonstrated the superiority of PET/CT over PET and CT alone in the staging and restaging of

cancer. [17]-[18]-[19] PET/CT imaging equipments are not available everywhere and it is very costly to buy machine and cost of the investigation is cheap, whereas, gamma camera and 99mTc-MDP bone scan is available with low cost. 99mTechnetium methylene diphosphonate (99mTc MDP) bone scintigraphy is currently the method of choice for the detection of bone metastases. Bone scintigraphy is still the work-horse of nuclear medicine in the search for bone metastasis in patients with malignant tumors, especially breast cancer. Bone scintigraphy is widely available, relatively inexpensive, and highly sensitive in the detection of bone metastasis. The high sensitivity correlates with a lower specificity because many benign conditions, such as degenerative joint disease, infections, and benign bone tumors, exhibit increased uptake of radiotracer.

V. CONCLUSIONS:

In this series of breast cancer patients 99mTc-MDP scintigraphy proves highly sensitive but less specific in measuring the extent of bone metastasis in breast cancer. It elucidates, non-invasively, lesion characteristics and indicative for prognosis and response to chemotherapy and hormonal treatment. Therefore, bone scanning with 99mTc-MDP has clinical value in the detection of bone metastases. Bone is the most common site of breast cancer metastasis (70%) can be detected before it appear in conventional radiography.

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Figures: Total (5)

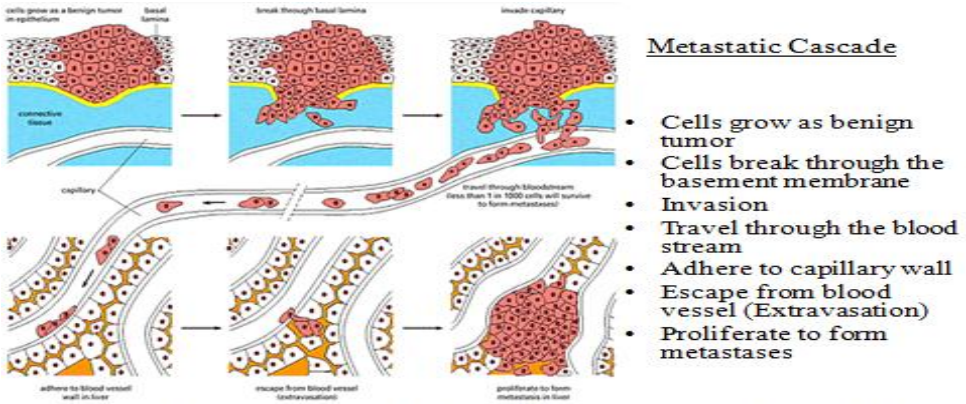

Figure: Process of Metastasis: *Alberts, B. (Bruce Alberts) et al. Molecular Biology of the Cell , 4th ed., New York: Garland, 2002, p. 1325*

Figure 1: Diagram showing molecular biology of the cells and process of bone metastases.

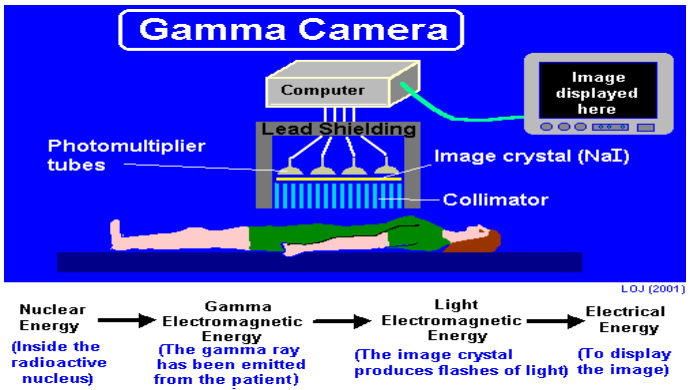

Figure 2: Schematic diagram of Single head Gamma camera with patients and image display on computer

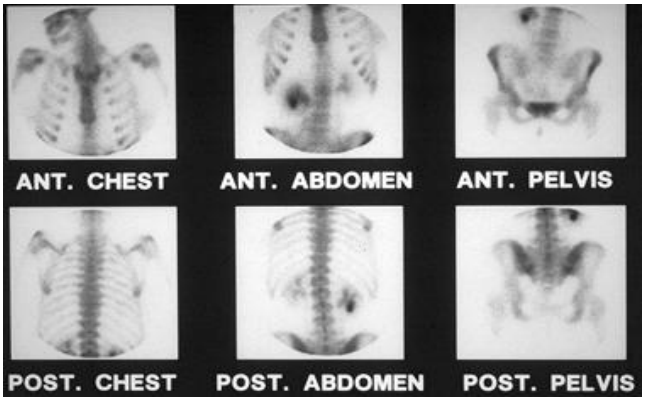

Figure 3: Normal Bone scan - Static views (spot) of 99mTc-MDP Skeletal scintigraphy show symmetrical distribution of radiotracer in the skeleton.

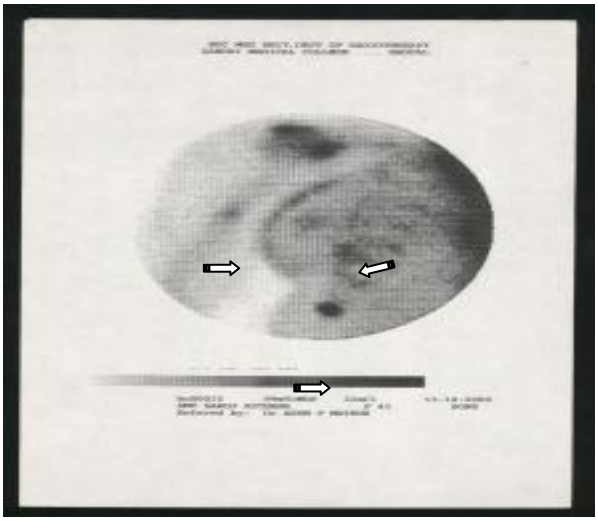

Figure 4: 99mTc-MDP bone scintigraphy showing increased radio-tracer in the sites of bone metastases in right humerus, right ribs and primary of breast cancer patient (Arrows).

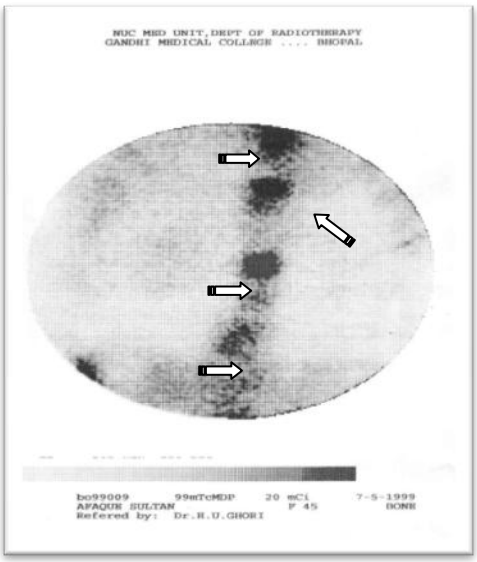

Figure 5: Static view of vertebrae's and lumbo-sacral joints, 99mTc-MDP bone scintigraphy showing increased radio-tracer in the sites of bone metastases in D-12,L-1,L-3 and L-5 vertebras (Arrows)of breast cancer patient.

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