

The Use of Radio Tracers in Nuclear Medicine: Seeing the Unseen, a Review

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ABSTRACT:

The purpose of this paper is to illustrate the variety of breast lesions that can be recognized using various molecular imaging methods, provide pertinent information on correlative anatomic imaging, and assist the reader in obtaining further imaging as necessary. In order to stage and plan treatment for breast cancer patients, Tests related to nuclear medicine, including fluorine 18 (18F) fluorodeoxyglucose (FDG) PET/CT, lymphoscintigraphy, and bone scans, may be performed. In patients without breast cancer, focal or diffuse radiotracer uptake may also be discovered by chance within the breast. In order to help validate a suspected diagnosis, these findings could be clinically important and associated with mammograms or breast US, thereby saving the patient more worry and workup. One radiotracer may be clearly absorbed by some lesions whereas another is not absorbed at all. Knowing the typical amount of radiotracer uptake for particular breast lesions may also help with accurate diagnosis.

KEYWORDS: Lymphoscintigraphy, body bone scintigraphy, 99m Technetium-Sestamibi, 99mTc-methylene diphosphonate (MDP), Radioiodine, 18F-FDG Imaging.

I. INTRODUCTION

The main element impacting the prognosis and treatment options for patients with breast cancer is the tumor cells' ability to spread to axillary lymph nodes [1]. The likelihood of metastasis is directly influenced by the tumor's size [2,3]. New cases of breast cancer generally present with a smaller original lesion because early detection of mammary lesions is now achievable because to advancements in imaging techniques and screening exams. On the other hand, there is still a great demand for diagnostic non-invasive or minimally invasive techniques that offer precise preoperative staging of the lymph node status. With the help of a gamma-detecting probe, lymphoscintigraphy is simple to perform and has been used successfully in melanoma patients [4] and, more recently, in patients with breast cancer

[5]. The lymphoscintigraphic imaging technique has the advantage of identifying the node and determining the exact position of the skin incision. A sentinel node's metastases are classified according to size: isolated tumor cell clusters (pN0i1) when 0.2 mm or smaller and containing no more than 200 tumor cells in a single cross section; macrometastases when larger than 2 mm; and micrometastases (pN1mi) when larger than 0.2 mm but no more than 2 mm. This nomenclature is applicable to both immunohistochemistry and traditional staining (6).

In cases of advanced breast cancer, the most frequent location for metastatic disease is the skeleton. A bone lesion is the first site of metastasis in 26% to 50% of patients with metastatic breast cancer, and bone metastases occur in around 30% to 85% of individuals with metastatic breast cancer. [7-9] Breast cancer patients most frequently develop solitary metastatic bone disease in the sternum (34%), pelvic (18%), thoracic spine (16%), lumbar spine (10%), ribs (7%), and pelvis, with the skull and femur following closely behind [10, 11]. The majority of individuals with a single bone metastasis during an extended follow-up period go on to develop metastases at other locations.

Breast cancer patients may have nuclear medicine tests for staging and therapy planning, such as bone scans, lymphoscintigraphy, and fluorine 18 (18F) fluorodeoxyglucose (FDG) PET/CT. In patients without breast cancer, focal or diffuse radiotracer uptake may also be discovered by chance within the breast. These results might be clinically significant and could be correlated with breast US or mammograms to help confirm a suspected diagnosis, thereby saving the patient more anxiety and workup. It is possible for some lesions to have strong uptake of one radiotracer but no uptake of another. Making the right diagnosis may also be aided by knowledge of the typical degree of radiotracer uptake of particular breast lesions. Gallium 68 (68Ga) tetraazacyclododecane tetraacetic acid octreotate (DOTATATE), 18F-fluciclovine, and 68Ga-prostate-specific membrane

antigen (PSMA) are among the PET radiotracers that may also show incidental breast uptake.

BONE SCINTIGRAPHY:

The most used technique for detecting bone metastases is wholebody bone scintigraphy [12–13]. It can detect elevated blood flow and osteoblastic activity in the afflicted region. Because they provide the advantage of whole body imaging at a relatively low cost, technetium Tc 99m (^{99m}Tc)-labeled bisphosphonates, such as hydroxymethylene diphosphonate dicarboxypropane diphosphonate or methylene diphosphonate [^{99m}Tc-MDP], are the most often used in the treatment of cancer patients.

WBBS detects the metabolic response of bone that takes place in trauma, inflammation, degenerative processes, and malignancy. [14–18]

WBBS is more sensitive than radiography for identifying early bone metastases (44% to 50%). [19] Single-photon emission CT (SPECT) and SPECT/CT, which provide 3-D imaging and can produce axial, sagittal, or coronal images, can be used to further assess equivocal results on WBBS. [20]

Multislice CT, which offers comprehensive anatomic information, is a feature of contemporary SPECT/CT scanners.

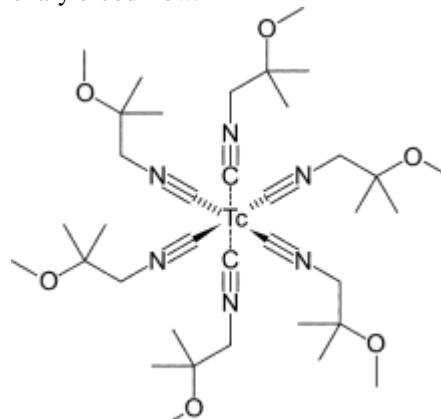
Because SPECT/CT can identify the structural features of lesions and has a higher lesion to background contrast, it increases the sensitivity and specificity for detecting bone metastases. [21] When compared to SPECT alone and SPECT and CT with side-by-side readings, SPECT/CT enhances the receiver operating characteristics (ROCs) and inter-reporter agreement for the diagnosis of bone metastases [22]. Because SPECT/CT provides a more accurate diagnosis, fewer needless follow-up studies are conducted. [23-24]

SPECT and Planar Scintigraphy:

^{99m}Tc Sestamibi:

When assessing hyperparathyroidism, technetium ^{99m}Tc (99mTc)-sestamibi is utilized for myocardial perfusion imaging and parathyroid adenoma localization. To get to the mitochondria, it diffuses passively throughout the cell and is lipophilic. (25). ^{99m}Tc-sestamibi diffuses into myocardial cells from the circulation and is stored in the mitochondria during myocardial perfusion imaging. The radiotracer is helpful in assessing myocardial perfusion and identifying coronary

artery dysfunction since its extraction rate is related to coronary blood flow.



Normally functioning parathyroid glands do not absorb more sestamibi in endocrine imaging, but parathyroid adenomas feature oxyphil cells with many mitochondria that have a high uptake and slow release of sestamibi. ^{99m}Tc sestamibi is taken up by a variety of malignancies, including breast cancers, and can be unintentionally found on scans for hyperparathyroidism or myocardial perfusion. The uptake of sestamibi studies may be higher for infiltrating lung cancer, ductal carcinoma in situ, and intraductal carcinoma (26). Actually, the US Food and Drug Administration has approved ^{99m}Tc-sestamibi for the diagnosis of breast cancer. These investigations, which are sometimes referred to as breast-specific gamma imaging or molecular breast imaging, have demonstrated sensitivity of up to 95% and specificity of up to 80% (27). On ^{99m}Tc-sestamibi scans, benign breast lesions such as fibroadenomas and fibrocystic disease can also be detected, however their uptake may vary.

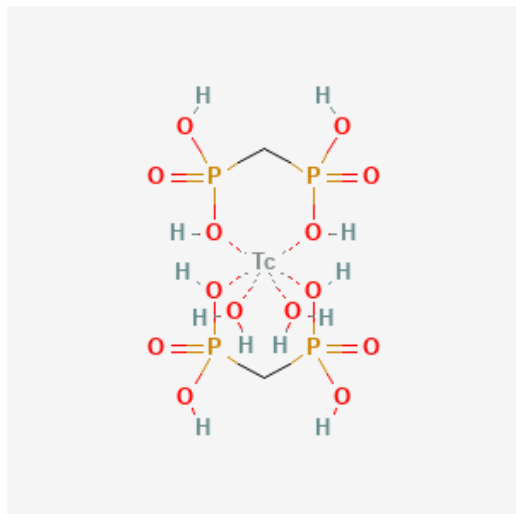
Bone Scan using ^{99m}Tc-Methylene Diphosphonate:

A frequent nuclear medicine study used to assess infections, injuries, malignancies, and metastatic disease is the bone scan.

An intravenous injection of ^{99m}Tc-methylene diphosphonate (MDP) may be followed by imaging 2-4 hours post-injection for a single-phase investigation.

^{99m}Tc-MDP accumulation rises in areas of enhanced bone production or repair due to increased blood flow and osteoblastic activity. ^{99m}Tc MDP attaches itself to bone through chemisorption with the osseous matrix's hydroxyapatite (25). It can also attach itself to

amorphous calcium phosphate in the ossification or calcification of soft tissues.



As part of their metastatic workup, patients with breast cancer may have a bone scan. The breast cancer itself exhibits uptake, which could be brought on by ^{99m}Tc -MDP attaching to soft tissue calcifications or necrotic tumors. More traditionally, patients with diffuse osseous metastatic illness show higher absorption in several specific sites across the skeleton.

On a bone scan, primary breast sarcoma may also show higher uptake, which may be connected to the existence of microscopic calcification (28). Tensely elevated uptake can also be seen in primary or metastatic osteosarcoma, a breast tumor that forms bone (29,30). Metastases from the gastrointestinal tract, lung, kidney, thyroid, and skin have been seen in the breast, despite the fact that this is an uncommon location of metastasis.

There have also been reports of benign processes showing higher uptake on bone scans, including fibroadenomas, fibrocystic disease, lactational change, gynecomastia, breast implants, hematomas, and fat necrosis (31). Collagen deposition, inflammation, local metabolic abnormalities, and/or increased blood flow are some of the uncommon causes of MDP accumulation.

Scans using Radioiodine:

Iodine comes in a number of radioactive isotopes, the most widely used of which are ^{131}I (^{131}I) and ^{124}I (^{124}I). The thyroid gland uses iodine, an important element, to make thyroid hormone (32). The sodium-iodine transporter on the cell surface allows iodine from the bloodstream

to enter the thyroid follicular cells. Following oxidation, thyroglobulin molecules are added to the iodine to organize it. Other organs that produce the sodium-iodine transporter can also absorb iodine and may need it for metabolism or excretion. Fat necrosis, gynecomastia, supernumerary breasts, lactational duct cysts, or galactoceles are some of the causes of the 6% of nonlactating women who have increased ^{131}I breast uptake (33). One possible explanation for the elevated ^{131}I uptake in fat necrosis is inflammation and scarring. Because of elevated sodium iodine transporter expression, benign tumors such as fibroadenomas may have higher ^{131}I uptake. The sodium iodine transporter is also expressed by breast tumors, although they might not concentrate iodine as much as the thyroid gland.

Positron Emission Tomography:

^{18}F -FDG Imaging:

^{18}F -FDG, a glucose analog, is widely used to evaluate various cancer types. Compared to normal tissue, cancer cells have higher rates of glucose metabolism, which enables them to absorb more ^{18}F FDG (34). Following intravenous injection, After passing through the glucose transporter membrane proteins (GLUT1), the enzyme hexokinase phosphorylates ^{18}F -FDG. Normal phosphorylated dietary glucose can be further metabolized by glycolysis or glycogen production, while phosphorylated ^{18}F -FDG cannot and becomes trapped inside cancer cells(35,36).

GLUT1 transporter and hexokinase expression, the number of viable tumor cells, the histologic subtype, tumor vascularity, cell proliferation, and the presence of inflammatory cells can all influence the amount of ^{18}F -FDG absorption in breast malignancies (37).

Larger, higher grade, triple negative, or estrogen receptor negative breast tumors typically have higher ^{18}F -FDG uptake. In breast malignancies, a higher risk of recurrence and a worse prognosis are linked to higher ^{18}F -FDG uptake (38). In addition, ductal carcinoma in situ and infiltrating lobular carcinoma have reduced ^{18}F -FDG uptake in comparison to intraductal carcinoma.

Breast cancer staging and therapy response monitoring are two applications for ^{18}F -FDG PET/CT. Bone scans and CT scans of the chest, abdomen, and pelvis are recommended by the National Comprehensive Cancer Network for patients with early-stage I or II breast cancer. In patients with operable stage III, stage I, or stage II

breast cancer, 18F-FDG PET/CT is not usually recommended. It is optional to use 18F-FDG PET/CT for patients with stage IIIA illness or above (39). Ultimately, for the routine staging of patients with breast cancer, 18F-FDG PET/CT cannot take the role of contrast-enhanced diagnostic CT (40).

Mastitis, fibroadenomas, and gynecomastia are additional benign reasons for elevated breast uptake on 18F-FDG PET/CT scans. In the affected locations, mastitis will be diffusely absorbed.

Although fibroadenomas usually show little to no FDG uptake, they might show elevated FDG uptake that resembles cancer.

68Ga-DOTATATE Imaging:

A relatively novel PET radiotracer called 68Ga-DOTATATE is utilized to image neuroendocrine tumors like meningiomas, paragangliomas, and pheochromocytomas (41). Similar to indium 111 (111In)-octreotide, which has long been employed in neuroendocrine tumor imaging, 68Ga-DOTATATE interacts to somatostatin receptors on the cell surface of neuroendocrine tumor cells. 68Ga-DOTATATE has a lower radiation dose, better resolution, and faster absorption than 111In-octreotide. Osteoblastic activity, inflammation, splenosis, and the pancreatic uncinate process are all examples of false-positive or physiological absorption of 68Ga-DOTATATE.

Increased 68Ga-DOTATATE uptake has been observed in up to 50% of breast tumors and other nonneuroendocrine cancers, such as meningioma, follicular thyroid adenoma, non-Hodgkin lymphoma, and papillary thyroid cancer (42). A mass with focally elevated 68Ga-DOTATATE uptake can also be a sign of metastatic neuroendocrine tumors to the breast (43). For treatment planning purposes, it's critical to distinguish between a primary breast cancer and a neuroendocrine tumor metastases when focal breast uptake is detected. SUVmax of 3.3 may be shown by an incidentally discovered breast cancer at 68Ga-DOTA-NOC (DOTA 1-Nal3-octreotide) PET/CT, a comparable radiotracer analog, and 2.8 by associated metastatic axillary lymph nodes (44).

Lactating women's breasts can accumulate 68Ga-DOTATATE, which is subsequently eliminated in breast milk. Generally speaking, lactational alterations manifest as somewhat elevated diffuse radiotracer uptake (45). It is advised that a lactating woman receiving 68Ga-DOTATATE PET/CT refrain from nursing for four

hours following the study,(46) then express and discard any breast milk before continuing to breastfeed in order to reduce the radiation exposure to the kid.

68Ga-PSMA Imaging:

The relatively new PET radiotracer 68Ga-PSMA binds to PSMA, which is expressed on prostate cell membranes. The kidney, liver, spleen, small and large intestines, and lacrimal and salivary glands all exhibit physiological uptake of 68Ga-PSMA. PSMA is overexpressed in primary and metastatic prostate cancer (47), but it is also overexpressed in lung, thyroid, colon, esophageal, renal cell carcinoma, and brain tumors. Additionally, 68Ga-PSMA can attach to breast cancer and its metastases (48,49). It's possible that breast cancer metastases will absorb more 68Ga-PSMA than the original tumor. Different patients' breast cancers and different lesions within the same patient can have varying degrees of 68Ga-PSMA uptake.(50,51)

Benign conditions such sarcoidosis, Paget disease of the bone, schwannoma, thyroid adenoma, benign breast tissue, gynecomastia and pseudoangiomatous stromal hyperplasia have also been shown to express PSMA. Up to 75% of men with prostate cancer after antiandrogen therapy experience gynecomastia because their estrogen levels are comparatively higher than their testosterone levels; these individuals are frequently scanned using 68Ga-PSMA. Gynecomastia usually manifests as bilateral diffuse breast tissue expansion accompanied with moderate 68Ga-PSMA uptake. Histologic sampling of the lesion is necessary to prevent misinterpreting a benign breast mass with elevated 68Ga-PSMA uptake as malignant.

18F-Fluciclovine Imaging:

The most popular PET-radiolabeled amino acid tracer for prostate cancer is 18F-fluciclovine, which is also relatively recent (52). Cells absorb it via sodium-dependent transporters of amino acids. Moderate pituitary and salivary uptake, variable mild-to-moderate intestinal activity, and intensive uptake in the liver and pancreas are all characteristics of normal biodistribution. Early pictures show moderate bone marrow and minor muscle activity, with the latter rising over time and the former decreasing. Prostatic hyperplasia, inflammation, infection, and metabolically active benign bone lesions like osteoid osteoma are

among the benign processes that can result in 18F-fluciclovine uptake .

The imaging of head and neck tumors, breast, lung, and cerebral gliomas has also been investigated using 18F-fluciclovine. Despite having varying levels of 18F-fluciclovine uptake, people with recurrent prostate cancer may develop breast cancer concurrently (53). When compared to benign lesions such post-treatment scarring, fibroadipose tissue, and fibrocystic alteration, breast malignancies have noticeably higher 18F fluciclovine absorption (54,55).

Histologic subtypes such invasive lobular carcinoma may exhibit enhanced uptake with 18F-fluciclovine in comparison to 18F-FDG, and aggressive breast tumors may exhibit comparatively higher uptake. 18F-fluciclovine has the ability to identify uptake in skeletal and nodal metastases, but its ability to assess hepatic metastases is constrained by the high physiologic background uptake.

II. CONCLUSION

Studies using PET nuclear medicine and scintigraphy may occasionally find a large number of benign and malignant breast lesions. There are a lot of new PET radiotracers being made available for clinical usage, which could result in more breast lesions being unintentionally discovered. It's critical to distinguish between primary breast neoplasms and metastatic lesions, as well as benign and malignant breast uptake. Knowing how breast lesions show on different imaging modalities can aid the radiologist in accurately diagnosing the condition, preventing needless follow-up, and, when necessary, recommending dedicated breast imaging.

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