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2.4. BREAST IMAGING BY Tc99m MIBI SCINTIGRAPHY: DIAGNOSTIC EVALUATION-DOSIMETRIC CONSIDERATION

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Breast cancer is the most common form of cancer amongst women and as a cause of death it ranks

The routine screening method includes physical examination and mammography but both have diagnostic limitations. Mammography is highly sensitive but poorly specific since only 15-30% of mammographically suspicious lesions that require surgical biopsy are proved to be histologically malignant (1).

A last- years approach on the subject is the scintigraphic imaging of the breast. A number of radiolabelled agents have been investigated as to their ability to demonstrate abnormalities in the breast, for example Tl-201 -chloride, Tc-99m-Sestamibi, In-111-octreotide or radiolabelled estradiol (2-10). However, breast scintigraphy, that it is performed after intravenous administration of Tc-99m sestamibi and includes planar and/or single photon emission computed tomography (SPECT) images, is the scintigraphic method that gains place and seems to be included as a screening test in the breast diagnostic investigation.

Scintimammography is a recently verified technique that expands the use of nuclear medicine to breast disease investigation. It delivers sensitivity as high as X-ray mammography for palpable tumors but with greater specificity. It is best used at patients in whom X-ray mammography, ultrasound and M R I prove non-diagnostic or unhelpful, particularly for those women with dense breasts or who have had previous breast surgery; It assists in identifying rnulti focal carcinomas in patients with diagnosis of breast cancer. May be useful in the evaluation of the effectiveness of neo adjuvant chemotherapy for breast carcinoma.

This study is referred to the role of Tc-99m methoxyisobutyl isonitrile (MIBI) scintimammography as a complementary procedure to conventional mammography for the detection of breast carcinoma. A diagnostic protocol based on the joint use of the two modalities could reduce the number of biopsies required for patients with suspected breast cancer. Tc-99m-MIBI is a cationic chemical complex that accumulates in myocardial tissue in proportion to regional coronary blood flow. The mechanism of uptake of Tc-99m - MIBI in breast tissue is only partly understood and in itself may help in determining important aspects of tumor function. The major metabolic pathway for clearance of Tc-99m-MIBI is the hepatobiliary system. About 27% of the injected dose is cleared through renal elimination after 24 hours and approximately 33% is cleared through the feces in 48 hours.

Dosimetric calculations were also performed for Tc-99m -Sestamibi since the use of this radiopharmaceutical, as radionuclide screening in breast cancer investigation, seems to increase. As with every new scintigraphic technique it is very important to deal with the dosimetrical aspect of the procedure i.e. to calculate the absorbed doses to the radiosensitive human organs. For this radiopharmaceutical the target organs of interest are the breasts, ovaries, lungs, kidneys, liver, gallbladder and bladder as well as the heart. As far as the breast is concerned a novel approach is introduced, based on the geometry of the thoracic region. For the other target organs dosimetric calculations are performed according to the MIRD scheme. Finally, scintimammography is dosimetrically compared to conventional mammmography, certainly characterized by a higher dose to the breast and scattered radiation that leads to higher dose absorption by sensitive organs.

METHOD

No special preparation for the test is needed; however, a thorough explanation of the test should be provided by the technologist or physician. The patient should remove all clothing and jewelry

above the waist, and should wear a hospital gown open in front. Recent mammograms should be available, as well as ultrasound, if performed.

A breast physical examination is performed by either the nuclear medicine physician or the referring physician. The time of last menses and pregnancy and lactating status of the patient should be determined. Breast scintigraphy should be delayed at least 2 wk following a cyst aspiration or fine needle aspiration, and 4 to 6 wk following a core or excisional biopsy.

Intravenous injection of 740– 1110 MBq (20-30mCi) Tc-99m sestamibi radiopharmaceutical is administered in an arm vein contra lateral to the breast with the suspected abnormality. If the disease is bilateral, the injection is ideally administered in a foot vein. Normal distribution of the radiopharmaceutical includes the salivary and thyroid glands, myocardium, liver, gall bladder, small and large intestine, kidneys, bladder, and skeletal muscles. A standard scintillation camera is equipped with a low-energy, high-resolution collimator and a symmetric, not greater than 10% (±5%), energy window should be centered over the 140 keV photopeak of Tc-99m in order to avoid maximum scattered radiation.

The patient lies prone with a single breast dependent from the imaging table. The contra lateral breast should be compressed against the table to prevent cross-talk of activity. A breast positioning device (table adaptor, foam pad, etc.) should be used, if this is possible, to minimize patient motion. The arms should be raised to expose the axillae. The detector should touch the patient's side for improved resolution. The anterior image may be acquired with the patient supine.

Imaging begins 5 – 10 min following administration of the radiopharmaceutical. Planar images are acquired for 10 min each, using a 256 x 256 matrix to allow for pixel overload that may come from the liver, heart, etc. Two hours post injection delayed images are repeated at the same positions and by the same parameters.

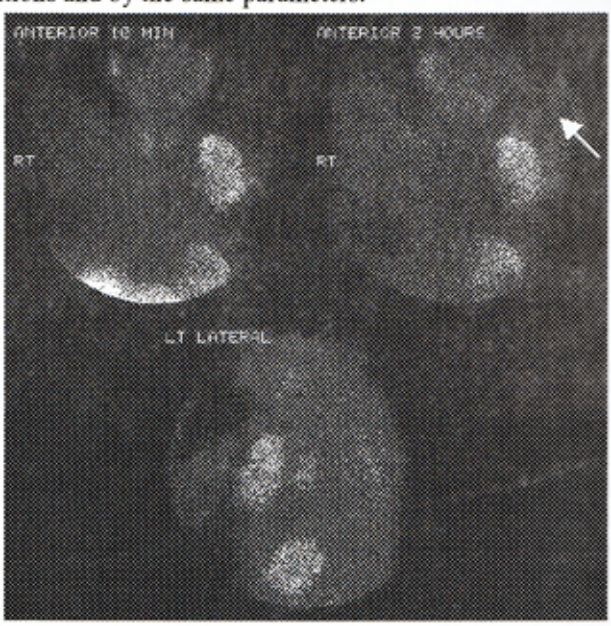

Image 1. Anterior and Left lateral prone 99mTc-MIBI scinti mammograms show extented breast cancer (white arrow) with no evident axillary involvement.

The following planar images should be acquired:

Prone lateral image of the breast with the suspected abnormality. The field of view should include the breast, axilla, and anterior chest wall, excluding any other internal organ activity. Electronic magnification should be used as needed to optimize pixel size. If needed, prone posterior oblique image of the ipsilateral breast should be performed, moving the detector 30 degrees posterior of lateral. Prone lateral and, if needed, posterior oblique images of the contra lateral breast could also be performed.

The anterior supine image should include both breasts and both axillae in the field of view. Magnification must not be used in anterior position if the camera system does not allow breasts and both axillae to be included in the image.

Spect Imaging of the breasts follows the planar images, in 180^0 rotation clockwise from right lateral to left lateral, in prone position.

Processing of the images may demand, for improvement of visualization of breast tissue, the masking of the high-activity chest and abdominal organs, such as the myocardium and liver, from

the final images. This masking may be performed using regions of interest generated on the computer or by count subtraction. Both the masked and original images should be included in the final display.

RESULTS

Interpretation of the images should be done from the computer monitor whenever possible, as adjustment of the image contrast by the interpreting physician may be necessary. A logarithmic scale to enhance low-count areas instead of a linear scale is preferable for image display. Sometimes Gray scale is preferable to color for interpretation.

Interpretation Criteria

* Focal increased uptake of the radiopharmaceutical in the breast or axilla (in the absence of radiopharmaceutical infiltration) is suspicious for malignancy.
* Mild homogeneous uptake of the radiopfaannaceuilcal in the breast or axilla is consistent with a normal study.
* Diffuse or patchy radiotracer uptake of mild to moderate intensity, often bilateral with edges not well-defined visually, are features more suggestive of a benign disease of the breast and is probably not consistent with malignancy.
* There is a great variability of intensity of focal uptake. The following image features are more suspicious of breast malignancy:

Focal increased uptake, unilateral, relatively well-delineated contours, with mild to intense radiotracer uptake; focal increased uptake (one or more foci) in the ipsilateral axilla, in the presence, of a primary lesion in the breast is strongly suggestive of axillary lymph node metastatic involvement. Note that a linear and superficial axillary uptake on the lateral thoracic views usually corresponds to uptake in skin folds (32-34).

Artifacts

Infiltration of the radiopharmaceutical administered in an arm vein may cause false positive uptake in the axillary lymph nodes. Patient positioning which does not allow the breast to be fully dependent will decrease the accuracy of the test. Patient motion will decrease the accuracy of the lest. If both breasts are dependent, cross-talk of activity may result in a false positive result in the contra lateral breast.

The sensitivity, specificity and accuracy of this test depend upon several factors including the size of the breast tumor being imaged. The sensitivity of this test for tumors under 1 cm in diameter is very low with current nuclear medicine cameras in use (35-36),

Dosimetric Consideration

The complementary role of mammary scintigraphy to the routine diagnostic modalities is nowadays recognised (11). However, further investigation is needed in order to establish it as a screening method and to this perspective even dedicated devices are under consideration (12).

It is not sufficient to show abnormal data by the above new scintigraphic technique. It must also be shown that this method is safe, with low radiation burdening and is characterised by a lower probability of missing malignancies in comparison to other established diagnostic techniques. The use of radiation in Medicine is involved in all the stages of cancer screening, diagnosis and therapy. In all cases dose measurement is one of the most important steps, as the benefit that the patient gains from radiation use, should by far outweigh the potential harmful effects of radioactivity.

In radiodiagnosis and radiation therapy the source of radiation is external and therefore it is easy to measure doses in a phantom or in-vivo using suitable dosimeters (13). In Nuclear Medicine however, things are completely different. *The* source of radiation is internal and the precise

calculations of absorbed doses require knowledge of pharmakocinetics, complex modeling and methods. For each new scintigraphic technique new mathematical models have to be developed in order to achieve a good approximation to the actual absorbed dose (14). This particular task is critical, as in Nuclear Medicine there is no ability of measuring absorbed doses in-vivo or even in a phantom. When a new technique is investigated it is of vital importance to consider its dosimetrical aspect and perform the necessary calculations.
Scintimammography is a relatively new technique for the detection of breast cancer and a number of radiopharmaceuticals are being under evaluation. However, it has not yet been dosimetrically evaluated, while the breast, as an organ is not included in the MIRD tables (15,16).
Absorbed dose calculations are more critical for this test as women suffering from breast cancer are likely to receive an increased radiation dose during diagnosis, therapy and follow-up.

Dosimetric technique
Dosimetric calculations are performed for Tc^{99m}-Sestamibi as the radiopharmaceutical of choice in breast scintigraphy (2,17-20).
Scintimammography is performed with the patient prone and the breast compressed or with the patient supine. These particular positions ensure the decrease of breast thickness in order to have less scattered radiation from the breast tissue (21-22). The injected activity is usually SOOMBq Tc^{99m}-Sestamibi (2,4,6,19).
In breast dosimetry calculations (15,16) radiopharmacokinetics are critical. Specifically, kinetic modelling (23) was a useful component of estimation of cumulated activity in various source organs in the body. Tc^{m}-Sestamibi is a cationic chemical complex that accumulates in myocardial tissue in proportion to regional coronary blood flow. The major metabolic pathway for clearance of Tc99m-Sestamibi is the hepatobiliary system. (13,14) About 27% of the injected dose is cleared through renal elimination after 24 hours and approximately 33% is cleared through the feces in 48 hours (26). Dosimetric calculations are performed according to the MIRD system. The formulation assumes that the activity is uniformly distributed in the source organs. The masses assumed for organs and tissues of the body are available from the MIRD publications (15,16). The calculations are based on tabulated values of absorbed dose per unit cumulated activity at the organs of interest. These values designate the fraction of" energy emitted from the source organ that is deposited to the target organ. The size, shape, composition and density of the organs influence these quantities. The MIRD scheme makes the assumption that the radionuclide is uniformly distributed within each source organ and only enables the determination of an average dose to each target organ considered. Their evaluation is based on Monte Carlo calculations used with an anthropomorphic phantom in which the body organs are represented by a simplified geometric model not always accurate representation of them. Though the method is considered adequately accurate statistically, we have to bear in mind that there remain many cases, mentioned in MIRD pamphlets (15,16) in which the coefficient of variation exceeds 50%. A bask assumption necessary for the use of the MIRD tables is that the cumulated activity is uniformly distributed in the source organ. However as far as the breast is concerned the MIRD tables do not provide any data. A new approach, simple to its concept and easy to perform is introduced here. Based on the relative positions of the breast and lung (Fig.l) in the human body it is assumed that the radiation reaching the breast is approximated by the radiation accumulated after the lung has absorbed its fraction (27,28).
The lung is modeled as half an ellipsoid (fig.l) and I is the essential width of the lung, i.e. the mean value of Ii and 1_2. If d is the distance between the breast and lung tissue interfaces the dose absorbed by the breast is dependent on the the radiation incident oa the tang, the radiation transmitted unscattered through the lung and intermediate tissue between breast and lung as well as the radiation incident on the breast. The target organs of interest are the ovaries, breasts, lungs, kidneys, liver and bladder.

The effective half-life is calculated as a combination of the biological and physical half -lives. Biological half-life estimation is based on the biodistribution data available for this radiopharmaceutical.

Radiation interaction with air approximates very well the absorption characteristics of lung, while water is a good approximation of breast tissue. The tissues that occupy the intermediate space between lung and breast are muscle and bones, therefore the absorption characteristics of the intermediate medium is calculated as the mean value of the absorption coefficients characterizing the two tissues. The values of **l** and **d** are 10 and 2cm respectively (30).

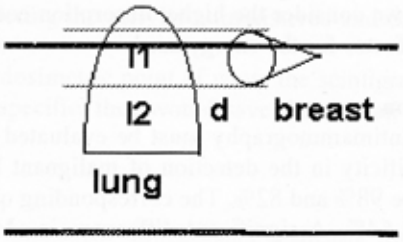

Fig. 1 Geometric representation of the lung and the breast

Tc^{99m}-sestamibi mainly accumulates in the hepatobiliary system and approximately 33% of the injected dose is cleared through the intestines in 48 hours. Renal elimination takes place for the 27% of the injected dose in 24 hours. The accumulation at the myocardium is 1.5% of the injected dose with an effective half-life of 7 hours (26).

DOSIMETRIC RESULTS

Based on the above data we consider as source organs the intestines, kidneys, liver, spleen and the heart as from the available biodistribution data these are the organs that concentrate the majority of the injected quantity. The absorbed dose to the breast is calculated with the mathematical model presented in the previous section.

TARGET ORGANS	D_{Tc99m} Absorbed Dose (10^{-2}mGy/MBq)
Ovaries	4.2
Lungs	3.2
Breasts	3.8
Kidneys	7.8
Liver	4.9
Bladder wall	7.0

TABLE I: Absorbed dose in mGy per unit activity of radiopharmaceutical injected intravenously (D in 10^{-2} mGy/MBq).

Radiopharmaceutical	Administered Activity	Organ Receiving the Largest Radiation Dose		Effective Dose	Total body Dose
	MBq (mCi)	Gall bladder mGy/MBq (rad/mCi)		mSv/MBq (rem/mCi)	mSv/MBq (rem/mCi)
Tc-99m-sestamibi	740 – 1110 i.v.	0.099	0.01	0.0026	
	(20 – 30)	**(0.37)**		**(0.04)**	**(0.0098)**

TABLE II: Radiation Dosimetry for Female Adult: Injected Activity of Tc99m-MIBI, max absorbed Dose in Gallbladder and the Effective Dose in Scintimammography by Tc99m Sestamibi

Mean mammography entrance doses are obtained from a survey performed in Britain (31), The mean entrance dose was 7mGy per projection. *The* precise calculation of absorbed dose would require exact knowledge of the absorption characteristics of the breast for the KeV used. However the mean entrance dose is a good indicator as the dose absorbed by the breast will certainly be higher if we consider the higher absorption coefficient that characterizes it relatively to air and the build up factor for the energy used.

Discussion

MIBI scintimammograpby must be evaluated visually by the 2 hours late images. Its sensitivity and specificity in the detection of malignant breast lesions has been found, by different authors (36), to be 98% and 82%. The corresponding quantitative results were according to the late images 95% and 64%, A significant difference in MIBI accumulation was also found to represent the grade of malignancy. In the detection of metastatic lymph node involvement, the sensitivity and specificity with MIBI were 53% and 81%.

In calculations of absorbed doses, our selection of the source organs was based on pharmacokinetic data available, whilst that of the target organs OD their radiosensitivity (27). From Table I it is evident that the dose to the ovaries and liver does not differ considerably,

The urinary system constitutes a basic elimination pathway for this agent, The relatively higher dose to the kidneys and bladder, resulting from the use of Tc^{m} Sestamibi, can be attributed to the long residential life of the radiopharmaceutical in these two organs.

However, it is important to mention thai the method of extrapolating tie dose to the breast does not account for scattered radiation. The assumption that the energy reaching the breast is just the part of primary radiation passing through the lung is a source of uncertainty.

The derivation of a more realistic model for the breast that will account for the scattering effects by neighboring organs, is not an easy task. The mathematical analysis of such a model brings in multiple scattering theory and therefore very complicated analytical and computational techniques and the improvement in the accuracy of absorbed dose calculation is not critical (27) as the contribution of scattered radiation to the dose absorbed by the breast is small.

The doses from mammography test are, as expected higher. That applies not only for the breast itself but also for other organs owing to the scattered radiation. The value of 7mGy per projection (31) represents a mean dose and is derived from measurements of dose levels at 24 mammography units. The doses measured actually ranged from 4.6 to 9,5 rnGy per projection. The variation *in* dose levels depends highly on the status of the mammography unit, the film used and all tie parameters affecting the radiographic procedure. The higher doses from mammography, as well as the variation depending on the unit are well known facts. However, they are considered acceptable as the particular test is the most reliable routine screening method for breast cancer and the experience gained on it by now makes it irreplaceable for the time being.

However the development of scintigraphic tests for the detection of breast cancer is of great importance not only from a dosimetric point of view. As research shows a radiomiclide scan could provide information on the staging of the disease as weli as to its diagnosis considering that it may also be applied to the staging of axillary lymph node involvement (17).

Mammography is certainly characterized by a higher dose to the breast and scattered radiation leads to higher dose absorption by sensitive organs. Still, mammography is a reliable screening test and the one of choice up to now, owing to the high experience that has been gained so long.

CONCLUSION

The complementary role of mammary scintigraphy to the routine diagnostic modalities must be recognized. However, further investigation will show the possibility of its establishment as a screening method and to this perspective, dedicated devices are under consideration. Further study is needed to determine the characteristics of the population most likely to benefit from breast scintigraphy.

A new mathematical approach for the calculation of absorbed dose to the breast during Scintimammography is introduced. With an easy and convenient method a fairly good approximation of actual dosirnetric figures is achieved. The radiation burden calculated by the new method for the breast and with the MIRD scheme for the other target organs has been found to be of the order of mGy/MBq, low enough considering the activity administered and comparing to the absorbed dose received during marnmography,

Compared to conventional mammography, from a dosimetric point of view, the scintigraphic test burden would be less and provided that it is highly specific, they would save the woman screened from further tests.

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