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The Role of Molecular Imaging Technologies in Breast Cancer Diagnosis and Management

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1. Introduction

Anatomic breast imaging techniques such as mammography and ultrasound are very useful in the detection of breast cancer, but can have limited sensitivity and positive predictive value, particularly in patients with dense breasts (Kolb et al., 2002). These limitations have provided the impetus for adjunctive technologies such as nuclear medicine and PET based diagnostic imaging procedures. The nuclear medicine based technique is referred to as Breast-Specific Gamma Imaging (BSGI) or molecular breast imaging (MBI) while the positron-emission tomography (PET) based technique is referred to as Positron Emission Mammography (PEM). Both have demonstrated good results in clinical studies and are increasingly being adopted into clinical practice. Although these imaging techniques have similarities, they are different in several aspects. This chapter is designed to provide an overview of these imaging technologies and their potential roles in patient management.

2. Radiotracers

Both BSGI/MBI and PEM are physiologic imaging modalities conducted through the injection of a pharmaceutical, called a tracer, which is tagged with a radioactive isotope and the resulting molecule is called a radiotracer. Each radiotracer is designed to bind to a specific target (organ, tissue, physiologic process, cell receptor or protein) while the isotope tag emits radiation that is detected by cameras placed near the patient. The cameras provide an image of the distribution of the radiotracer tracer and thus measure a specific physiologic process in the area being imaged.

2.1 Isotopes

There are two types of radioactive isotope tags used in medical imaging: single gamma emission isotopes and positron emission isotopes. Single gamma emission isotopes release a gamma ray from the nucleus. There are a variety of single gamma isotopes used in nuclear medicine. The most common isotopes used in diagnostic imaging are referred to as low-energy isotopes with gamma-ray energies ranging from 80 – 200 kiloelectron volts (keV). The gamma ray is a photon with sufficient energy to exit the body and be captured by specially designed detectors called gamma cameras. Positron emission isotopes emit a

positron, an antimatter particle with the same mass as an electron, but with a positive charge. This positron travels a short distance from the nucleus prior to colliding with an electron. Since the positron is a particle traveling through the tissue until this collision, the patient radiation dose associated with positron emission isotope studies is generally higher than that from single gamma emission isotope examinations. This collision results in annihilation of both particles converting the mass of the two particles into energy and producing a pair of 511 kiloelectron volt (keV) gamma rays traveling approximately 180° from each other. In positron emission tomography imaging (PET) these gamma rays exit the body and are captured by a pair of opposed gamma cameras.

The units for measuring the activity of radiotracer delivered to the patient are the Becquerel and the Curie. The Becquerel (symbol Bq) is the SI-derived unit of radioactivity. One Bq is defined as: one decay (emission) per second. The curie (symbol Ci) is a unit of radioactivity, defined as 3.7×10^{10} decays per second. In breast imaging, the megabecquerel (MBq) and millicurie (mCi) are the most common units used; one millicurie equals 37 Megabecquerel. These units only describe the number of decays per second for a given sample and are not to be confused with the units used to describe the radiation dose they deliver to a patient. A more detailed discussion of radiation dose is provided in Section 4.

2.1.1 Pharmaceuticals for BSGI/MBI

BSGI/MBI is a single photon imaging technique that has been conducted using a variety of imaging agents, but the most common is ^{99m}Tc-hexakis-2-methoxyisobutylisonitrile also referred to as ^{99m}Tc-Sestamibi or MIBI. MIBI is a 140 KeV gamma ray emitting isotope in a lipophilic cation molecule. It was originally cleared by the US FDA for use as a cardiac perfusion agent; breast imaging was subsequently added subsequently breast imaging was added as an indication following additional clinical studies to determine its efficacy in this application. It is injected intravenously and is retained in cells likely by electronegative cellular and mitochondrial membrane potentials (Piwnica-Worms et al., 1990). Studies show that its accumulation is roughly proportional to blood flow, desmoplastic activity and cellular proliferation and therefore it accumulates preferentially in breast cancers compared with surrounding tissues (Cutrone et al., 1998). It is a lipophilic substrate for the P-glycoprotein (Pgp), a cellular efflux pump for various compounds (Ballinger et al., 1995). Therefore, Sestamibi exhibits rapid tumor wash-in (within about 2 minutes) followed by a slow tumor washout (over the course of several hours) (Sciuto et al., 2002). Based on these factors, imaging can begin within minutes after injection and can continue for up to about 90 minutes post injection, providing ample time for all required views to be conducted before the washout cycle negatively impacts lesion-to-background tracer concentration ratio. In addition, since the level of Pgp expression correlates with tumor response to cytotoxic chemotherapy, a comparison of immediate and delayed images (4 hours post injection) may be used to quantify the radiotracer washout as a measure of Pgp expression and the probability of multi-drug resistance.

There are no known contraindications for use. Reactions to Sestamibi are generally minor according to the Cardiolite drug data sheet. In the analysis of potential reactions, 3068 patients (77% men, 22% women, and 0.7% not recorded) were documented from the cardiac clinical trials and 673 were recorded from the breast imaging trials. Of the 673 breast imaging patients, all of whom were women, the most common reported reaction was taste

perversion with most of those patients reporting a metallic taste at the time of injection. The other minor reactions are listed in table 1. More serious reactions were reported in less than 0.5% of patients and included: signs and symptoms consistent with seizure occurring shortly after administration of the agent; transient arthritis, angioedema, arrythmia, dizziness, syncope, abdominal pain, vomiting, and severe hypersensitivity characterized by dyspnea, hypotension, bradycardia, asthenia, and vomiting within two hours after a second injection of Technetium Tc99m Sestamibi. However the list of serious reactions is from the total population of patients including men and women undergoing a cardiac stress test.

Body System	N = 673
Body as a whole	21 (3.1%)
Headache	11 (1.6%)
Cardiovascular	9 (1.3%)
Angina	0 (0%)
ST segment changes	0 (0%)
Digestive System	8 (1.2)
Nausea	4 (0.6%)
Special Senses	132 (19.6%)
Taste Perversion	129 (19.2%)
Parosmia	8 (1.2%)

Table 1. Reactions to Sestamibi from 673 breast imaging patients.

2.1.2 Pharmaceuticals for PEM

PEM is a positron emission imaging technique conducted with 2-[fluorine-18] fluoro-2-deoxy-D-glucose (FDG), a modified glucose molecule with a positron-emitting isotope. Breast cancers exhibit a greater uptake of FDG than the surrounding breast tissue due to their hyperglycolytic rate. For some malignant lesions, although they possess an elevated GLUT-1 transmembrane transport function, however this does not necessarily result in increased tracer uptake (Smith, 1999). Studies have established that the uptake of FDG is primarily dependent on blood flow, the type of breast malignancy and the microstructure of the lesion (nodular vs. diffuse) (Avril et al., 2001). For example, lobular carcinoma exhibits a roughly 30% lower uptake than ductal carcinoma (Avril et al., 2001). For the PEM procedure, patients must fast 4 – 6 hours prior to the injection of FDG. It is important to note that patients with compromised glucose metabolism should have their glucose level checked prior to the administration of FDG and at least one study reports that altered glucose metabolism can affect the sensitivity of this procedure (Berg et al., 2006). FDG is administered intravenously and imaging is conducted approximately 60-90 minutes post injection in order to allow sufficient time for glucose uptake into the tissue. Patients should be requested to sit quietly in a dark, calm room to avoid manipulating the distribution of FDG. A dual-phase imaging technique may be used to improve specificity of the study (imaging at both 60 and 90 minutes post injection).

The emitted positron has a mean free path of approximately 1 mm in the breast tissue before annihilation with an electron resulting in the emission of two 511 KeV gamma rays. The random nature of the displacement between the positron and gamma ray points of origin

has some impact on the lower limit of spatial resolution in studies using positron-emitting isotopes (Turkington, 2001).

2.2 Comparison of BSGI/MBI and PEM Radiotracers

Both Sestamibi and FDG demonstrate increased accumulation in breast cancers, although the mechanism for this accumulation is better understood for FDG. In addition, although the breast tissue typically has a homogeneous uptake of both tracers, they can accumulate in normal glandular tissue resulting in a diffuse heterogeneous uptake pattern, especially in pre-menopausal women who are in the luteal phase of their menstrual cycle (Lin et al., 2007). This is not surprising as it reflects the heterogeneous nature of the breast tissue and the impact of blood hormone levels on the breast parenchyma. This heterogeneity does not generally impact cancer detection, but may complicate interpretation. The intensity of this pattern can be reduced for both tracers by imaging outside of the luteal phase and several studies report that day 2 – 14 of the menstrual cycle is optimal. Neither tracer is linked to nephrogenic systemic fibrosis, a sometimes fatal condition that is associated with gadolinium contrast agents used in breast MRI. MIBI has some minor pharmacologic considerations and rare reactions occurring in less than 0.5%of patients. FDG imaging requires fasting for a minimum of 4 hours prior to injection and as mentioned in the previous section, it is beneficial to check the blood glucose level prior to FDG administration as the tumor uptake of FDG is reduced in hyperglycemic states (Schelbert et al., 1999) and this results in some potential for complications and reduced sensitivity for the procedure in diabetic patients. In comparison, MIBI does not require fasting and imaging can be conducted within minutes of the injection.

Some of the physical and clinical differences between FDG and MIBI imaging are summarized in Tables 2 and 3 respectively.

	Energy of Emission photon	Half Life (minutes)
FDG	511 KeV	110
MIBI	140 KeV	360

Table 2. gamma-ray emission information for radiotracers.

	Pre-study Fasting	Injection to Imaging time	Recommended Pre-procedural testing
FDG	4 - 6 hours	60 – 90 minutes	Blood glucose
MIBI	None	5 minutes	None

Table 3. Radiotracer administration and imaging considerations.

3. Imaging systems

Both the single gamma and positron isotopes described in section 2.1 ultimately emit gamma rays (the positron isotopes through the annihilation and the conversion of the positron) that exit the patient's body and can be detected with external detectors. The goal of

these detector systems is to reconstruct the gamma ray emissions into an image that allows the physician to visualize the distribution of the radiotracer in the body. There are two modes of image reconstruction, plannar and tomographic. The planar method results in a single 2-dimensional image per acquisition, similar to the mammogram. Tomographic reconstruction provides a 3-dimensional reconstruction of the breast similar to MRI. The single gamma detector systems used for BSGI/MBI can be planar or tomographic and can be constructed of a single or multiple detectors. The positron imaging systems used for PEM by their design provide tomographic imaging only and since the detection of the pair of gamma rays is required for image reconstruction, positron systems must consist of either a pair of opposed detectors or a ring detector design.

3.1 Gamma-ray imaging basics

The detection of an abnormality in BSGI and PEM imaging is based on the ability of the imaging system to depict the variations of uptake in the tissue. Unlike anatomical imaging where high spatial resolution is needed to visualize the detailed morphology used to provide differential diagnosis, the molecular imaging system must provide sufficient image contrast in order to visualize the variations in radiotracer uptake; the contrast between radiotracer concentration in the tumor and the uptake of the surrounding breast tissue. While this is partially a function of resolution, there are several other factors impacting imaging. This contrast based imaging requires a careful balance between spatial resolution, image noise and photon sensitivity. Generally, as spatial resolution increases, image noise increases and photon sensitivity decreases proportionally to some degree thus if spatial resolution is increased to a level where the detector has poor photon sensitivity and the resulting image noise is too high, the ability of the system to visualize the contrasting tissue uptake is diminished. A detailed discussion of the balance between these factors is beyond the scope of this text, but it is important to realize that in molecular imaging is a contrast based imaging and spatial resolution is not the only parameter affecting the visualization of lesions. For example, it is possible to detect a 1 mm cancer using a system with a 4 mm spatial resolution if the uptake of that lesion is sufficiently enough higher than the background to overcome the partial volume effect. Conversely, a 40 mm cancer could be missed by the same imaging system if the lesion uptake is not sufficiently higher than the surrounding tissue.

As an illustration, nearly all commercially available large field-of-view gamma cameras, typical to the nuclear medicine department, have a variable matrix setting, including 512 x 512, 256 x 256 and 128 x 128. Although the 512 x 512 setting produces the highest spatial resolution, nearly all nuclear medicine studies are conducted on the 256 x 256 or 128 x 128 settings because the resulting image noise at the 512 x 512 setting diminishes image quality for the majority of studies.

System photon sensitivity is another important parameter in BSGI/MBI and PEM imaging. As photon sensitivity increases, the amount of radiotracer, the length of time the image is acquired, or some combination of both parameters can be decreased. For Example: a given detector system is providing good clinical images using a dose of 300 MBq and an acquisition time of 10 minutes. If the photon sensitivity of this system can be increased 50% the clinician would have three possible options. First, they could reduce the patient's radiation exposure by reducing the amount of radiotracer delivered to the patient by 50%, to

150 MBq and maintain the same imaging time, 10 minutes. Second, they could reduce the imaging time by 50% to 5 minutes using a 300 MBq dose. Or third, they could reduce both the time and the dose by roughly 25% resulting in a dose of 225 MBq and an imaging time of 7.5 minutes. It is important to remember that in molecular imaging techniques such as BSGI/MBI and PEM, the imaging time and the dose delivered can be manipulated, but reducing both to any large degree is not possible unless significant improvements in photon sensitivity are obtained.

3.1.1 BSGI/MBI Imaging

BSGI/MBI imaging is conducted with a single-head or dual-head detector system (see Figure 1). Only one detector equipped with a collimator is required for image reconstruction. Generally, gentle breast compression (normally less than 12 lbs or 53 newtons) is used to provide breast immobilization. This compression is noticeably lower than that used in mammography for two reasons. First, the typical imaging time for a single BSGI/MBI image is significantly longer than that needed for a mammographic projection, 5 – 10 minutes, thus lower pressures are better tolerated by patients and second, the 140keV gamma ray emitted in BSGI/MBI has sufficiently higher tissue penetration than the 8 – 35 keV x-ray used in mammography therefore these images benefit less from higher compression. As shown in figure 1, in the single-head design a paddle is used to provide compression and in the dual-head system, the breast is compressed between the detectors. The compression paddle used in the single head system can be exchanged for a fenestrated paddle to allow biopsy. Biopsy is currently not available on the dual-head design.

Fig. 1. A single and dual head imaging system for BSGI/MBI.

3.1.2 BSGI/MBI detectors

As mentioned in the previous section, there is generally an inverse relationship between photon sensitivity and spatial resolution however both are important to imaging. These parameters are determined by several aspects of the detector design, especially that of the collimator. The most commercially available systems have an extrinsic spatial resolution of between 1.9 and 3.3 mm at the surface of the detector however it is important to note that the spatial resolution of planar, single gamma imaging systems decreases with increasing source-to-collimator distance, thus the spatial resolution of a lesion near the detector is better than that of one deep in the breast tissue, relative to the detector face. For example, if the breast is being imaged in the cranio-caudal position (detector inferior to the breast tissue), lesions in the inferior portion of the breast tissue will be somewhat more visible than

those in the superior portion of the breast. This resolution loss is, at least in part, the driving logic behind the dual-head opposed detector design. In theory, if the breast is imaged using a dual-head system in the cranio-caudal position, the upper detector would maximize visualization of the superior portion of the breast while the lower detector optimizes visualization of inferior lesions.

Although there is a theoretical benefit to the dual-head design, it is interesting to note that clinical data from the dual-head and single-head systems shows similar performance in terms of lesion sensitivity (see section 5 below). This is likely due to the two-view imaging protocol adopted from mammography that is standard in BSGI/MBI protocols. Just as in mammography, the optimal coverage of breast tissue is obtained by acquiring an MLO and CC image of each breast and additional images are obtained as needed. Since all patients have a minimum of two views obtained, the likelihood of a lesion being deep to both projections is quite small. In addition, similar to mammography, when a lesion is seen in only one image, additional images are obtained in order to determine the location of the lesion in the breast tissue. As long as this two-view protocol remains the standard, it is unlikely that the dual-head system will result in significant improvements in the sensitivity of the detection of breast malignancies. However, provided the two detector images are fused properly, it may be possible to reduce either the injected dose or the acquisition time to facilitate low-dose imaging or higher throughput on the imaging system.

Single photon emission computed tomography (SPECT) is a recent development in BSGI/MBI. Currently these devices are only available in the research setting (Williams et al., 2010). Additional research is needed to determine if dual-head image combination techniques or the implementation of SPECT imaging will provide a clear benefit to BSGI/MBI in terms of breast cancer detection. Such studies are underway, but the data is not yet available for analysis.

Fig. 2. Left and Center - a single-head BSGI/MBI system with a compression paddle used for positioning. The left image illustrates the cranio-caudal (CC) position and the center image illustrates the medial lateral oblique position (MLO). The right image illustrates the MLO position with the dual-head system where the compression paddle is replaced by a second detector.

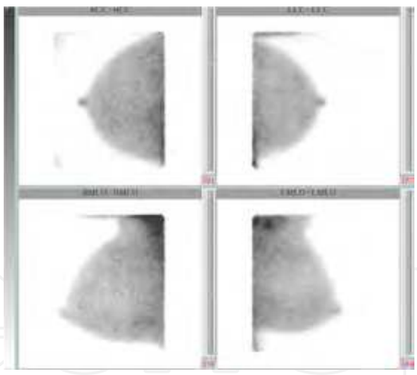


Fig. 3. A typical 4-view BSGI study.

3.1.3 Detectors for PEM

PEM imaging is conducted with either a dual head or ring style gamma-ray detector. Both systems are designed to detect the coincident gamma rays which, are traveling approximately 180° from each other after the annihilation reaction (see figure 4). Unlike BSGI imaging devices, PEM devices do not use a collimator to help determine the location of each event. In PEM imaging, since there are two gamma-rays traveling 180° apart, the event location is calculated as a line of response between the location that each gamma-ray strikes the pair of opposed detectors. One advantage to PEM is that it does not have the same loss of resolution with distance that BSGI/MBI systems experience. As mentioned in the previous section, the mean free path of the ^{18}F positron within the breast tissue is approximately 1 mm and commercially available PEM systems report an in-plane spatial resolution of about 2 mm. One limitation of the dual-head PEM detector design is that, due to the limited angle of acquisition, it has limited resolution in the Z-axis (depth). Ring detectors do not suffer from this limitation as they provide a 360° acquisition for reconstruction however there is currently no biopsy capability on the ring detector systems. A needle biopsy localization device was recently introduced for the opposed dual-head detector system.

Fig. 4. The left image provides an example of an opposed dual-head imaging system while the system on the right is an example of a ring detector system.

One limitation to PEM image reconstruction is that the detector photon sensitivity is not linear across the field-of-view with lower sensitivity along the detector edges. This causes a higher level of noise to be present in the breast images, along the chest wall. Figure 5 provides a schematic representation of factors affecting the photon sensitivity in a PEM detector. The maximum angle of reconstruction (MAR) is a setting used in PEM software and it is defined as the maximum angle away from the detector normals (90° from the detector face) for which coincident gamma ray detections are included in tomographic image reconstruction. Larger MAR values yield greater overall photon sensitivity but with potential loss in spatial resolution due to the depth-of-interaction (DOI) blur. The blue lines in Figure 1 show the angular range over which gamma rays emitted from two points in the breast are accepted. Figure 1A shows a point near the nipple, and Figure 1B shows one near the chest. For events that occur in the center of the field-of-view (FOV), all of the events within the MAR are captured by the detector system. However a significant fraction of events occurring near the FOV edges go uncounted for because one of the paired gamma rays traveling outside the edges of the detector is not detected. As a recent study found, this loss of photon sensitivity along the edges limits the ability of the PEM system to detect lesions located near the chest wall (Rosen et al, 2005).

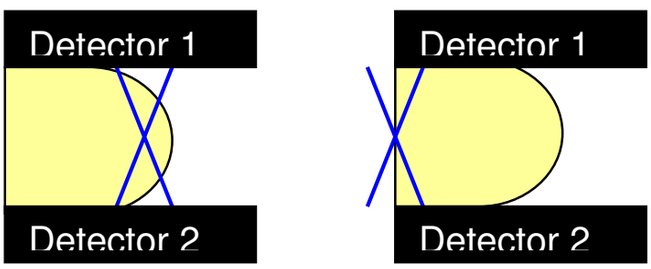


Fig. 5. A and B: a schematic example of the maximum angle of reconstruction near the center of the detector field-of-view and then near the chest wall respectively.

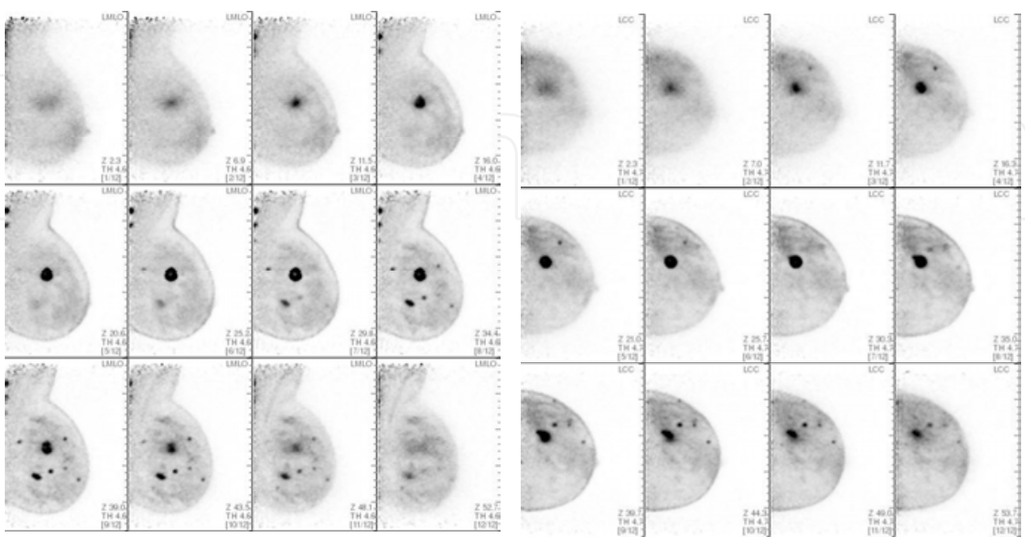


Fig. 6. a typical PEM study with multiple slice reconstruction for each projection.

PEM detectors are tomographic imaging devices, an example image from the opposed detector system is provided in Figure 6. Note the noise level along the chest wall and the Z-resolution affect is expressed as a blurry, low intensity focus in the reconstruction planes outside of the plane the lesion is located in. In this particular case, it is most noticeable in the MLO projection images. There is noticeable residual blur in the area of the largest lesion in all of the projections, including those outside of the lesion.

4. Radiation dose

As with all nuclear medicine procedures, the detector systems do not emit radiation. The radiation dose delivered to the patient in these procedures comes from the radiotracer and is dependent on both the activity of the radiotracer injected and the biologic distribution of the tracer in the organs.

4.1 BSGI/MBI radiation dose

Sestamibi (MIBI) was cleared by the US FDA in 1991 for cardiac perfusion studies. In 1997, breast imaging was added as an indication to the drug package insert following a clinical trial conducted with standard gamma cameras equipped with high-resolution collimators. According to the drug package insert, the patient whole-body radiation dose is 4.8 milligray at 1110 megabecquerels (0.5 rads at 30 millicuries), see Table 4. According to the Dosage and Administration section of the drug package insert, breast imaging is to be conducted using a dose of 740 – 1110 MBq (20 – 30 mCi).

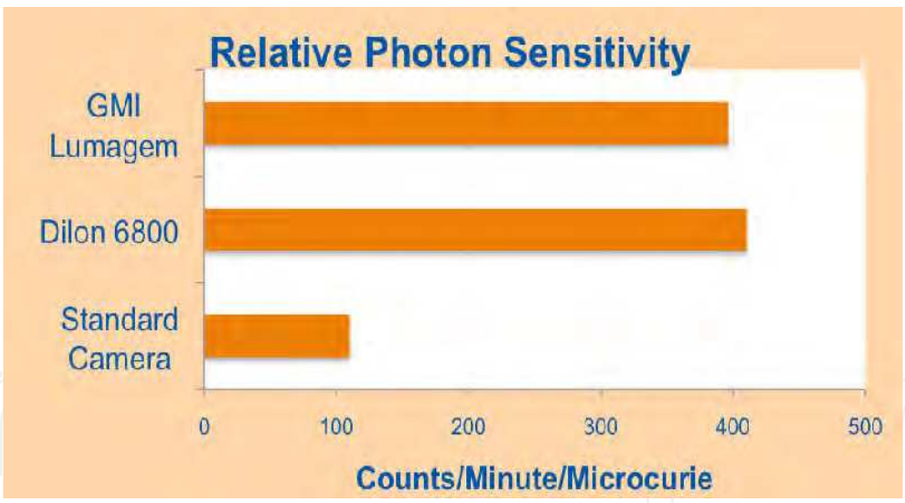
At the time of the US FDA approval, the breast imaging studies were being acquired with standard, large field-of-view gamma cameras, typical to a nuclear medicine department and the dose required for imaging was determined largely by the low photon sensitivity of these imaging systems when equipped with high-resolution collimators (Khalkhali et al., 2004) Since that time, several breast optimized gamma camera systems have been developed with significantly higher photon sensitivity and several studies indicate that it is possible to lower the injected dose of MIBI required for breast imaging with these systems.

A recent clinical trial was conducted to examine breast tissue uptake as a function of injected dose. The results of this analysis indicate that breast tissue uptake of MIBI appears to be linear relative to the injected dose thus implying there is no physiologic limitation to using lower doses (Böhm-Vélez et al., 2011). According to additional studies, conducted by the Mayo Clinic, the new, breast optimized detector systems provide a photon sensitivity roughly 3 times higher than that of the older imaging systems (Hruska et al., 2008).

From the available data, it is evident that these new detector technologies can reduce the dose required to conduct breast imaging with MIBI. Reducing the dose MIBI from 740 – 1110 MBq (20 – 30 mCI) to 259 – 370 MBq (7 – 10 mCi) reduces patient radiation exposure by nearly a factor of 3. The radiation exposure from a 259 MBq injection of MIBI is approximately 2 millisieverts (mSv) and is approximately equivalent to the radiation dose diagnostic breast patients receive from the combination of screening and diagnostic mammograms (Hendrick, 2010; Valinten, 2007).

Estimated Radiation Absorbed Dose				
	STRESS			
	2.0 hour void		4.8 hour void	
Organ	rads/ 30 mCi	mGy/ 1110 MBq	rads/ 30 mCi	mGy/ 1110 MBq
Breasts	0.2	2.0	0.2	1.8
Gallbladder Wall	2.8	28.9	2.8	27.8
Small Intestine	2.4	24.4	2.4	24.4
Upper Large Intestine Wall	4.5	44.4	4.5	44.4
Lower Large Intestine Wall	3.3	32.2	3.3	32.2
Stomach Wall	0.6	5.3	0.5	5.2
Heart Wall	0.5	5.6	0.5	5.3
Kidneys	1.7	16.7	1.7	16.7
Liver	0.4	4.2	0.4	4.1
Lungs	0.3	2.6	0.2	2.4
Bone Surfaces	0.6	6.2	0.6	6.0
Thyroid	0.3	2.7	0.2	2.4
Ovaries	1.2	12.2	1.3	13.3
Testes	0.3	3.1	0.3	3.4
Red Marrow	0.5	4.6	0.5	4.4
Urinary Bladder Wall	1.5	15.5	3.0	30.0
Total Body	0.4	4.2	0.4	4.2

Table 4. Radiation dosimetry of Sestamibi.



Graph 1. The relative photon sensitivity of commercially available, breast-optimized imaging systems compared to that of the standard gamma camera.

4.2 PEM radiation dose

F-18 fluorodeoxy-D-glucose (FDG) was cleared by the US FDA in 2000 for a variety of uses including tumor localization. The total body radiation dose in FDG PET is 39 mrads per mCi injected activity (Table 5). According to the clinical literature, the typical FDG dose used for imaging with the standard whole body PET detectors ranges between is approximately 370 - 740 MBq (10 - 20 mCi).

TABLE 5. RADIATION DOSE FOR INTRAVENOUS 2FDG(F-18) TO VARIOUS ORGANS

Target organ	Activity per organ (μCi/organ*)	From target organ (mrad/mCi)	From total body (mrad/mCi)	From bladder (mrad/mCi)	Total dose to target organ (mrad/mCi)
Kidneys	8	46.5	37.0	1.18	85
Lungs	25	40.9	35.1	1.52	78
Liver	30	37.2	37.1	0.887	75
Spleen	12	120.	37.1	0.718	160
Red marrow	15†	12.3	35.1	3.84	51
Ovaries	0.1	13.7	37.0	1.90	53
Testes	0.3†	13.5	38.8	15.6	68
Bladder‡	—	—	—	—	440
Brain‡	—	—	—	—	80
Heart	36	134	24.1	—	160
Total body	700	—	33.3	5.9	39

* Based on 1 mCi injection for percent injected activity from Table 1.
† Estimate based on relative weight: 1.5% of dose to red marrow and 0.03% of dose to testes.
‡ The radiation dose to the brain and to the bladder wall for 2-hr void time were evaluated in humans. See Tables 2 and 4.

Table 5. Radiation dose for FDG based on 1 mCi injection.

The dose of FDG used for PEM studies has generally followed the guidelines established with the lager systems, typically using approximately 444 MBq (12 mCi) (Berg et al, 2006). However, more recent studies have demonstrated that doses of 111 – 185 MBq (3 – 5 mCi) are possible with the breast-optimized imaging systems (MacDonald et al, 2010). The resulting radiation dose to the patient is 1.9 – 3.1 mSv using a low dose protocol, nearly identical to that of low dose BSGI/MBI (O'Connor et al., 2010).

5. Clinical evidence

There is a substantial history of clinical literature on imaging breast cancers with nuclear medicine techniques. One of the first reports of breast imaging using MIBI was provided by Campeau and his colleagues in 1992 while the first report of breast cancer imaging using FDG was reported by Wahl the previous year (Campeau et al., 1992; Wahl et al,. 1991) Since that time, hundreds of articles have been published on breast imaging using these radiotracers. However until recently, these imaging studies were conducted with large gamma cameras typical in the nuclear medicine department. The development of breast-optimized detector systems used in BSGI/MBI and PEM is more recent and the primary advantage of these systems is that they provide higher sensitivity for the detection of breast lesions than their predecessors.

5.1 Clinical evidence for BSGI/MBI

There have been several clinical studies evaluating BSGI/MBI in breast cancer detection. In 2008, the group from George Washington Medical University provided an overview of their experience using BSGI/MBI in 146 patients who participated in an IRB approved trial (Brem et al., 2008). Table 6 provides the reported sensitivity of BSGI for various subgroups from that analysis.

Overall	96%
Invasive Cancers	97%
Sub-centimeter lesions	89%
Lobular Carcinoma	93%
DCIS	94%

Table 6. The sensitivity of BSGI in various subgroups.

Other, larger studies have provided evidence of high sensitivity and specificity for BSGI. The first of these larger studies was an analysis performed by Weigert and her associates in more than 500 women who had a BSGI scan performed as part of their routine diagnostic imaging following conventional imaging (Weigert et al., 2007). It is interesting to note that over half of the patients in this study had indeterminate findings following mammography and ultrasound. Two years later, Bertrand presented the results from a retrospective, multicenter study reporting that BSGI provided a higher sensitivity than diagnostic mammography in detection of breast cancer, especially in the high-risk and dense breast populations (Bertrand et al., 2009) Last, in 2011, Lee et al reported that BSGI had a higher sensitivity than mammography and higher specificity than ultrasound in their series of 622 patients who had all three imaging modalities performed as part of their diagnostic examination (Lee et al., 2011). In addition, this work found that there was no change in the sensitivity of BSGI between normally dense and heterogeneously or very dense breast tissue.

	Bertrand, 2009	**Lee, 2011**	**Weigert, 2007**
Total Patients	1,042	662	512
Sensitivity (%)	91	95	89
Specificity (%)	77	88	90
NPV (%)	96	97	98

Table 7. The clinical performance of BSGI from several studies.

5.2 Clinical evidence for PEM

One of the earliest published studies on PEM containing a group of 77 patients examined the effectiveness of PEM in the detection of breast carcinoma (Berg et al., 2006). Table 8 provides the sensitivity of PEM as determined by this work. As expected, the sensitivity for lobular carcinoma was somewhat lower potentially due to the reduced glucose metabolism compared to ductal carcinoma.

	Sensitivity
Overall	90%
DCIS	91%
ILC	75%
Sub-centimeter	63%

Table 8. Sensitivity of PEM by sub-group.

The overall sensitivity and specificity for PEM is very good, especially for DCIS. Table 9 lists for each of the four PEM studies cited, the total number enrolled, the sensitivity, specificity, and negative predictive value.

	Berg, 2006	Tafra, 2005	Schilling, 2011
Total Patients	77	44	182
Sensitivity (%)	90	89	85
Specificity (%)	86	NR	74
NPV (%)	88	NR	NR

Table 9. Clinical results of PEM imaging. NR = not reported.

In clinical studies of BSGI/MBI and PEM, both of these metabolic imaging modalities provide improved sensitivity and specificity for the diagnosis of breast cancer compared to mammography alone. The sensitivity and specificity of BSGI and PEM are generally comparable with both modalities demonstrating the capability to visualize lesions as small as 1 – 2 mm. Both PEM and BSGI/MBI systems have biopsy guidance capabilities.

6. Clinical considerations

Both BSGI and PEM provide valuable clinical information in the detection and treatment of breast carcinoma. Like all imaging studies, each has distinct advantages and limitations. From the clinical data, it is evident that the performance of these modalities is quite comparable.

The biggest differences between the procedures are logistical. First, in most areas, MIBI is more readily available and significantly less expensive than FDG. In addition, the shorter half-life of FDG puts tighter constraints on the clinical schedule. For example, if a patient arrives 1 hour late for a FDG injection, the dose has lost 32% of the intended activity where as a MIBI dose has lost 9%. Also, the use of FDG requires four hours of patient fasting prior to injection and MIBI does not have this constraint. FDG also requires a 1-hour post-injection delay for imaging where as MIBI imaging can begin immediately post injection. Based on the injection-to-imaging time considerations, total time required for a MIBI study is approximately 45 minutes compared to approximately 2 hours for an FDG study.

7. Clinical indications

Several indications for these technologies have been proposed in the medical literature. Generally speaking, BSGI/MBI has been examined as a diagnostic adjunct to mammography and ultrasound when these imaging modalities are inconclusive or discordant with other imaging studies and/or clinical signs and symptoms and there is a remaining diagnostic concern. In addition, there is good data to suggest that it is also useful in pre-operative treatment planning for patients with known malignancy and in monitoring the response of the breast lesion(s) to neoadjuvant chemotherapy, see section 5.1. The majority of studies on PEM have examined its use as in preoperative treatment planning for patients with know malignancy and in monitoring the response of breast tumor(s) to neoadjuvant chemotherapy.

In June of 2009, an interdisciplinary committee established by the American College of Surgeons published a report to provide guidance on the use of imaging techniques in breast patients (Silverstein et al., 2009). This panel grouped BSGI/MBI and PEM together as molecular imaging techniques and issued the following recommendation:

- "The available information suggests that they (BSGI/MBI and PEM) may have equivalent sensitivity and improved specificity when compared with breast MRI. It is recommended that these adjunctive tools be used only after high-quality standard imaging is performed; their results should not prevent performing a biopsy recommended after conventional imaging. Either breast-specific gamma imaging or positron emission mammography may be used as an alternative to breast MRI when MRI is not available or is contraindicated in a particular patient. Both tools may be valuable in pre-operative surgical staging. Breast-specific gamma imaging may also be useful as an additional problem-solving tool in some situations."

7.1 Recognized BSGI/MBI indications

In June 2009, the Society of Nuclear Medicine released the Procedural Guidelines for Breast Scintigraphy with Breast-Specific Gamma Cameras that included several proposed several indications for BSGI/MBI (Goldsmith et al., 2009). The indications are quite specific and echoed those set forth by the American College of Surgeons. The indications can be grouped into 4 primary categories.

1. As a diagnostic adjunct for patients with indeterminate findings on conventional imaging (mammography, ultrasound and/or MRI) and remaining diagnostic concerns such as palpable mass, nipple discharge, pain, etc.
2. Preoperative treatment planning in patients with a known cancer diagnosis to determine the extent of the primary lesion and to detect additional foci of disease.
3. As an alterative to breast MRI for patients whom MRI is indicated, but not possible; ferromagnetic implants, compromised renal function, etc.
4. Monitoring tumor response to chemotherapy.

7.2 Recognized PEM indications

There are no additional published guidelines for PEM other than those of the American College of Surgeons that essentially provided three indications:

1. Pre-operative treatment planning in patients with a known cancer diagnosis to determine extent of the primary lesion and to detect additional foci of disease.
2. To monitor the response of breast tumor(s) to neoadjuvant chemotherapy.
3. As an alternative to breast MRI in patients for whom MRI is indicated, but not possible; ferromagnetic implants, compromised renal function, etc.

8. Conclusion

BSGI/MBI and PEM are adjunctive molecular breast imaging technologies which are becoming more common in the breast center and they provide very similar performance in terms of sensitivity and specificity. The radiation dose associated with these imaging techniques is similar to that patients receive from other diagnostic imaging procedures such

as CT, PET and nuclear medicine thus their use is currently limited to the diagnostic patient population. However, several studies are underway to reduce the radiation dose to the level of screening mammography which will likely increase their utility to breast cancer screening in the asymptomatic population. The BSGI/MBI procedure is a useful problem-solving tool for patients with dense or complex breast tissue and an unresolved diagnostic concern following anatomical imaging procedures such as mammography and ultrasound. Both BSGI/MBI and PEM are useful in breast cancer patients to detect the extent of disease (additional occult multifocal or muticentric disease) and to monitor tumor response to neoadjuvant chemotherapy. PEM has the advantage of tomographic reconstruction and uniform spatial resolution with increasing tumor depth. In addition, for the breast cancer patient undergoing a PET/CT scan for staging, it is possible to conduct the PEM study following the PET/CT without an additional administration of FDG. The advantages for BSGI/MBI are superior photon sensitivity along the chest wall, fewer patient restrictions and the wider availability of MIBI (see the considerations section above).

9. References

Avril, N., Menzel, M., Dose, J., Schelling, M., et al. (2001). Glucose Metabolism of Breast Cancer Assessed by 18F-FDG PET: Histologic and Immunohistochemical Tissue Analysis. *Journal of Nuclear Medicine,* Vol.42, No.1, (January 2001), *pp.*9–16, ISSN 0161-5505

Ballinger, J.R., Hua, H.A., Berry, B.W., Firby, P. & Boxen, I. (1995). 99Tcm-Sestamibi as an agent for imaging P-glycoprotein-mediated multi-drug resistance: in vitro and in vivo studies in a rat breast tumour cell line and its doxorubicin-resistant variant. *Nuclear Medicine Communications.* Vol.16, No.4, (April 1995), pp. 253–257, ISSN 0143-3636

Berg, W.A., Weinberg, I.N., Narayanan, D., Lobrano, M.E., Ross, E., Amodei, L., Tafra, L., Adler, L.P., Uddo, J., Stein, W. & Levine, E.A. (2006). High-resolution fluorodeoxyglucose positron emission tomography with compression ("positron emission mammography") is highly accurate in depicting primary breast cancer. *Breast Journal*. Vol.12, No.4, (July 2006), pp. 309-323, ISSN 1524-4741

Bertrand. M., Lanzkowsky, L., Stern, L. & Weigert, J. (2009). Results of a Multi-Center Patient Registry to Determine the Clinical Impact of Breast-Specific Gamma Imaging: A Molecular Breast Imaging Technique. *Radiologic Society of North America Annual Meeting*. Chicago, Illinois, USA, November 29 – December 4, 2009.

Böhm-Vélez, M., Kieper, D.A., Williams, M.B., Chang, T.S., Ward, B.H. & Straka, M.R. (2011) A Clinical Evaluation of Breast Tissue Uptake of Tc99m-Sestamibi as a Function of Injected Dose. *Breast Cancer Imaging: State of the Art 2011 – Poster Abstracts, Journal of Nuclear Medicine*, Vol.52, No.4, (April 2011) pp. 660-675. ISSN 0161-5505, Washington D.C. USA, April 21-22, 2011.

Brem, R., Floerke, A., Rapelyea, J., Teal, C., Kelly, T. & Mathur, V. (2008). Breast Specific Gamma Imaging as an Adjunct Imaging Modality for the Diagnosis of Breast Cancer. *Radiology.* Vol.247, No.3 (June 2008), pp. 651-57, ISSN 0033-8419

Campeau, R..J, Kronemer, K.A. & Sutherland, C.M. Concordant uptake of Tc-99m sestamibi and T1201 in unsuspected breast tumor. (1992). *Clinical Nuclear Medicine,* Vol.17, pp. 936-937

Cutrone, J.A., Yospur, L.S., Khalkhali, I., Tolmos, J., Devito, A. & Diggles, L. (1998). Immunohistologic assessment of technetium-99m-MIBI uptake in benign and malignant breast lesions. *Journal of Nuclear Medicine.* Vol.39, No.3, (March 1998), pp. 449–453, ISSN 0161-5505

Goldsmith, S., et al. (2010). SNM Practice Guideline for Breast Scintigraphy with Breast-Specific λ-Cameras 1.0. Available from http://interactive.snm.org/docs/BreastScintigraphyGuideline_V1.0.pdf

Hendrick, E. (2010) Radiation doses and cancer risks from breast imaging studies. *Radiology*. Vol.257, No.1, (October 2010), pp. 246-53, ISSN 0033-8419

Hruska, C.B., Phillips, P.W., Whaley, D.H., Rhodes, D.J. & O'Connor, M.K. (2008) Molecular Breast Imaging: Use of a Dual-Head Dedicated Gamma Camera to Detect Small Breast Tumors. *American Journal of Roentgenology*, Vol.191 No.6, (December 2008) ISSN 1546-3141

Khalkhali, I., et al. (2004). Society of Nuclear Medicine Procedure Guideline for Breast Scintigraphy 2.0. Available from http://interactive.snm.org/docs/Breast_v2.0.pdf. (June 2004)

Kolb, T.M., Lichy, J. & Newhouse, J.H. (2002) Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. *Radiology*, Vol.225, No.1, pp. 165–175. ISSN 0033-8419

Lee, A., Lee, J., Chang, J., Lim, W., Kim, B., Lee, B. & Moon, B. (2011). The efficacy of Breast-Specific Gamma Imaging with 99mTc-Sestamibi in the diagnosis of breast cancer according to breast density for Korean women. *Yellow Sea International Medical Biennial symposium,* Kintex, Korea, January 22, 2011

Lin, C., Ding, H., et al. (2007) Correlation Between the Intensity of Breast FDG Uptake and Menstrual Cycle. *Academic Radiology,* Vol.14, No.8, (August 2007), pp. 940–944, ISSN 1076-6332

MacDonald, L., Luo, W., Lu, X., Wang, C. & Rogers, J. (2010) Low Dose Lesion Contrast on the PEM Flex Solo II. *Medical Physics, Proceedings of the Fifty-second Annual Meeting of the American Association of Physicist in Medicine*, Vol.37, No.6, (July 2010) Philadelphia Pennsylvania, USA, July 18-22, 2010. ISSN 0094-2405

O'Connor, M., Li, H., Rhodes, D.H., Hruska, C.B., Clancy, C.B., Vetter, R.J. (2010). Comparison of radiation exposure and associated radiation-induced cancer risks from mammography and molecular imaging of the breast. *Medical Physics.* Vol.37, No.12, (December 2010), pp. 6187-1689, ISSN 0094-2405

Piwnica-Worms, D., Kronauge, J.F. & Chiu, M.L. (1990). Uptake and retention of hexakis (2-methoxyisobutyl isonitrile) technetium in cultured chick myocardial cells. Mitochondrial and plasma membrane potential dependence. *Circulation,* Vol.82, No.5, (November 1990), 1826–1838. ISSN 0009-7322

Rosen, E., Turkington, T., Soo, M.S., Baker, J.A. & Coleman, R.E. (2005). Detection of Primary Breast Carcinoma with a Dedicated, Large-Field-of-View FDG PET Mammography Device: Initial Experience. *Radiology*, Vol.234, No.2, (February 2005), pp. 527–534. ISSN 0033-8419

Schelbert, H., et al. Society of Nuclear Medicine Procedure Guideline for Tumor Imaging Using F-18 FDG. Available from http://interactive.snm.org/docs/pg_ch28_0403.pdf. 1999.

Schilling, K., Narayanan, D., Kalinyak, J., The, J., et al. (2011). Positron emission mammography in breast cancer presurgical planning: comparisons with magnetic resonance imaging. *European Journal of Nuclear Medicine and Molecular Imaging*. Vol.38, No.1, (January 2011), pp. 23-36, ISSN 1619-7089

Sciuto, R., Pasqualoni, R., Bergomi, S., et al. (2002) Prognostic Value of 99mTc-Sestamibi Washout in Predicting Response of Locally Advanced Breast Cancer to Neoadjuvant Chemotherapy. *Journal of Nuclear Medicine,* Vol.43, No.6, (June 2002), pp. 745–751, ISSN 0161-5505

Tafra, L., Cheng, Z., Uddo, J., et al. (2005). Pilot Clinical Trial of 18F-fluorodeoxyglucose Positron-Emission Mammography in the Surgical Management of Breast Cancer. *American Journal of Surgery*, Vol.190, No.4, (October 2005), pp. ISSN 628-632. 0002-9610

Turkington, T. (2001). Introduction to PET Instrumentation. *Journal of Nuclear Medicine Technology*, Vol.29, No.1, (March 2001), pp. 1-8, ISSN 0091-4916

Silverstein, M., et al. (2009). Image-Detected Breast Cancer: State-of-the-Art Diagnosis and Treatment. *Journal of the American College of Surgeons*. Vol.209, No.4, (October 2009), ISSN 1072-7515

Smith, T.A. (1999). Facilitative glucose transporter expression in human cancer tissue. *British Journal of Biomedical Science.* Vol.56, No.4, (April 1999), pp. 285-292, ISSN 0967-4845

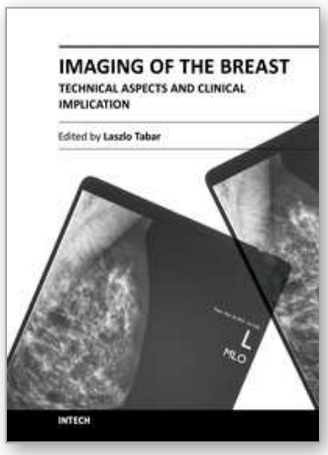
Wahl, R.L., Cody, R.L., Hutchins, G.D. & Mudgett E.E. (1991). Primary and metastatic breast carcinoma: initial clinical evaluation with PET with the radiolabeled glucose analogue 2-[F-18]-fluoro-2-deoxy-D-glucose. *Radiology*, Vol.179, No.3, (June 1991), pp. 765-770. ISSN 0033-8419

Weigert, J. (2007). Breast Specific Gamma Imaging (High Resolution Molecular Imaging of the Breast): A Useful Adjunct to Breast Imaging. *Radiologic Society of North America Annual Meeting*. Chicago, Illinois, USA, November 25–30, 2007.

Williams, M., Judy, P., Gunn, S., Majewski, S. (2010). Dual-Modality Breast Tomosynthesis. *Radiology,* Vol.255, No.1 (April 2010), pp. 191-198, ISSN 0033-8419

Valinten, J. (2007)The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. Ann ICRP 2007; Vol.37No.2-4, (March 2007) pp. 1–332. ISSN 0146-6453

Cardiolite Drug Data Sheet. Lantheus Medical Imaging Division. Available from http://www.cardiolite.com/pdfs/Cardiolite%20US%20PI%20513121-0710%207-20-2010.pdf



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Early detection of breast cancer combined with targeted therapy offers the best outcome for breast cancer patients. This volume deal with a wide range of new technical innovations for improving breast cancer detection, diagnosis and therapy. There is a special focus on improvements in mammographic image quality, image analysis, magnetic resonance imaging of the breast and molecular imaging. A chapter on targeted therapy explores the option of less radical postoperative therapy for women with early, screen-detected breast cancers.

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