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Scintimammography as an Adjunctive Breast Imaging Technology

An Evidence-Based Analysis

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Executive Summary

Objective

X-ray mammography (XMM) represents the most useful screening tool in breast cancer detection, especially for patients over 50. Unfortunately, XMM is not reliable in the assessment of dense breast tissue found in approximately 25% of women younger than 50 years of age, or in differentiating scar tissue from a tumor. Currently, ultrasound (US) is being used as an adjunct to XMM, with the purpose of improving sensitivity and specificity of XMM in breast cancer detection. In an attempt to reduce the biopsy rate resulting from false positive tests, other adjunctive technologies are being explored, including scintimammography (SMM). A number of papers in the current literature suggest the high value of SMM in breast cancer detection. This evaluation addresses the clinical indications for and effectiveness of SMM in the diagnosis of breast cancer.

The Technology

SMM is a nuclear medicine imaging technique that uses radionuclides and has the ability to image malignant breast tumors. SMM requires the administration of a gamma-ray emitting radiopharmaceutical to the patient, and a camera for imaging the lesion. The most commonly used radiopharmaceutical for SMM is TC-99m-methoxy isobutyl isonitrile MIBI.

Review Strategy

In the 2003 Medical Advisory Secretariat assessment of SMM in the diagnosis of breast cancer, a structured search was used to identify English-language studies published between 1992 and October 2002. A meta-analysis was then conducted of the literature which compared the diagnostic value of SMM with US as the second line imaging technique. An updated search strategy was developed in order to identify all studies published from October 2002 to January 2007.

Summary of Findings

The results of the meta-analysis showed that SMM is as effective as US in differentiating benign and malignant breast lesions. However, there may be a role for SMM as a third line adjunctive technique in the evaluation of breast abnormalities, in particular where breast ultrasound examination is inconclusive because of dense breast tissue or architectural distortion resulting from previous surgery or radiation treatment. There is equivalence between SMM and US as a second line investigation for abnormal mammograms. As of October 2003 (to January 2007), there was no new comparative evidence on the diagnostic accuracy of SMM and US as a second line diagnostic tool.

Conclusions

No new comparative evidence on the diagnostic accuracy of SMM and US as a second line diagnostic tool has become available between October 2002 and January 2007. Therefore, the conclusions from the 2003 MAS review remain for this updated version in 2007. The results of the meta-analysis showed that SMM is as effective as US in differentiating benign and malignant breast lesions. However, there may be a role for SMM as a third line adjunctive technique in the evaluation of breast abnormalities, in particular where breast ultrasound examination is inconclusive because of dense breast tissue or architectural

distortion resulting from previous surgery or radiation treatment. SMM is thought to be more accurate in patients with dense breasts, and as younger women are more likely to have dense breasts, a separate analysis specific to women under 50 years of age is needed.

Abbreviations

99mTc-sestamibi	TC-99m-methoxy isobutyl isonitrile MIBI
DCIS	Ductal carcinoma in situ
FNA	Fine needle aspiration
FPR	False positive rate
HRBGC	High-resolution breast-specific gamma camera
HRT	Hormonal replacement therapy
IDC	Infiltrating ductal carcinoma
ILC	Infiltrating lobular carcinoma
LCIS	Lobular carcinoma in situ
MRI	Magnetic resonance imaging
NPV	Negative predictive value
OBSP	Ontario Breast Screening Program
OCCI	Ontario Case Costing Initiative
PET	Positron emission tomography
PPV	Positive predictive value
ROC	Receiver operating characteristic
SEER	Surveillance, Epidemiology and End Results
SMM	Scintimammography
SPECT	Single photon emission computed tomography
SROC	Summary receiver operating characteristic
TPR	True positive rate
US	Ultrasound
XMM	X-ray mammography

Glossary

99mTc-sestamibi	A radionuclide that is accumulated in the mitochondria of tumor cells, which can then be imaged with a gamma camera
Ductal carcinoma in situ	Cancer cells that start in the ducts but have not penetrated the duct walls into the surrounding tissue. This is a highly curable form of breast cancer that is treated with surgery or surgery plus radiation therapy.
Infiltrating ductal carcinoma	The most common type of invasive breast cancer. It starts in the cells that line the milk ducts in the breast, grows outside the ducts, and often spreads to the lymph nodes.
Infiltrating lobular carcinoma	An invasive type of carcinoma of the breast characterized by linear growth into desmoplastic stroma around the terminal part of the lobules of the mammary glands; usually developing from lobular carcinoma in situ.
Lobular carcinoma in situ	A type of precancerous neoplasia found in the lobules of mammary glands, progressing slowly, sometimes to invasive lobular carcinoma after many years
Microcalcification	This refers to deposit of tiny amount of calcium in the breast tissue. It is visible as tiny spots on mammogram, and some patterns of micorcalcification in the mammogram are suggestive of cancer
Scintimammography	A nuclear medicine imaging technique that uses requires the administration of a gamma-ray emitting radiopharmaceutical to the patient, and a camera for imaging the lesion
Ultrasound	High-frequency sound waves are transmitted into the area of the body being studied and echoed back. The sound wave echoes are picked up and converted by a computer into an image that is displayed on a computer screen
X-ray mammography	A diagnostic technique that utilizes low-dose x-ray to find tumors in the breast; the resulting x-ray image is a mammogram

Objective

X-ray mammography (XMM) represents the most useful screening tool in breast cancer detection, especially for patients over 50. Unfortunately, XMM is not reliable in the assessment of dense breast tissue found in approximately 25% of women younger than 50 years of age, or in differentiating scar tissue from a tumor. Currently, ultrasound (US) is being used as an adjunct to XMM, with the purpose of improving sensitivity and specificity of XMM in breast cancer detection. In an attempt to reduce the biopsy rate resulting from false positive tests, other adjunctive technologies are being explored, including scintimammography (SMM). A number of papers in the current literature suggest the high value of SMM in breast cancer detection. This evaluation addresses the clinical indications for and effectiveness of SMM in the diagnosis of breast cancer.

Background

Clinical Need

Breast Cancer in Ontario

Cancer Care Ontario reported that breast cancer is the most common malignancy among Ontario women, representing 29% of all malignancies. It is the second leading cause of death for women following lung cancer, accounting for 19.4% of all cancer deaths among women in Ontario. In 2002, the National Cancer Institute estimated 7,800 new cases of breast cancer among Ontario women and 2,000 female deaths in the province from this disease (1).

The trend in incidence and mortality for breast cancer shows that there has been a small but steady annual increase in breast cancer incidence from 1973 to (estimates) for 2002. This increase leveled off in 1993 and the mortality rate for breast cancer has declined steadily since 1986. (1) This decrease is partially attributed to earlier diagnosis through effective screening programs.

Signs and Symptoms of Breast Cancer

Breast cancer may present with breast thickening, swelling, irritation or retraction of the skin, and nipple discharge, erosion, inversion or tenderness. Mammographic findings of malignancy include masses with associated architectural distortion, microcalcification or clustered microcalcification in a linear or branching array.

Classification of Breast Lesions

Malignant Tumors

Infiltrating ductal carcinoma (IDC) accounts for most newly diagnosed breast cancer cases. Ductal carcinoma in situ (DCIS) is defined as the transformation of ductal epithelial cells that are strictly contained within the breast and cannot, by definition, metastasize. The peak incidence of DCIS occurs between the ages of 40 and 60 years and most cases contain microcalcifications on imaging.

Infiltrating lobular carcinoma (ILC) arises in the small end ducts and has a poor prognosis. Lobular carcinoma in situ (LCIS) is multicentric in 60% to 80% of cases, is frequently bilateral {Haagensen CD, 1981 70 /id} and is diagnosed more commonly in younger women.

Medullary carcinoma is well circumscribed, and is often large and generally has a good prognosis. Colloid carcinoma is a slow growing invasive carcinoma that reaches large bulky proportion and occurs in older women (more than 70 years of age).
Table 1 demonstrates the incidence of each breast cancer type in Ontario women.

Table 1: Breast Cancer in Ontario by Histological Type 1992-1996*

Cancer type	Number of patients diagnosed	Percent
IDC	21,114	69.5%
ILC	2,474	8.1%
IDC & ILC	1,126	3.7%
Comedocarcinoma	692	2.3%
Mucinous adenocarcinoma	508	1.7%
Medullary carcinoma	451	1.5%
Other types	4013	13.1%
Total	30,378	100%

*IDC refers to Infiltrating ductal carcinoma; ILC, Infiltrating lobular carcinoma.
Source: Chiarelli, et al.; (2)

Benign Tumors

Benign breast tumors are classified as proliferative and nonproliferative. Nonproliferative benign tumors are not associated with an increased risk of breast cancer. Proliferative benign tumors without atypia are associated with 1.5 to 2.0 times increase in the risk of developing breast cancer.

Proliferative benign tumors with atypical hyperplasia are associated with a 4 to 5 times greater risk of developing cancer. (3)

Fat necrosis, which is a benign inflammatory process of adipose tissue and mammary fibromatosis, may mimic a breast cancer clinically, mammographically or sonographically.

Phylloides tumors are multinodular lesions and are classified as benign, borderline and malignant. (4)

Microcalcification

DCIS frequently manifests as microcalcification without an associated mass and accounts for as many as 50% of mammographically suspicious lesions. (5) The detection rate of DCIS has been reported as 6.2 cases per 100,000 women under 50 years, and 54.6 cases per 100,000 women older than 50 years. (6)

Multifocal or Multicentric Breast Cancer

Clinical examination alone, or in combination with US and/or fine needle aspiration (FNA) biopsy are less likely to detect multifocal disease.

Survival and Link to Early Diagnosis

Data from the United States Surveillance, Epidemiology and End Results (SEER) database shows that prognosis and survival are closely related to the stage of breast cancer at the time of diagnosis. (2) During the period from 1988 to 1991, the Ontario Breast Screening Program (OBSP) identified 39.1% of breast cancer cases as stage I (Table 2). SEER data in 1996 showed an increase in the percentage of cancers identified at stage I (increased from 40.9% between 1988 and 1991 to 46.6% in 1996). (2)

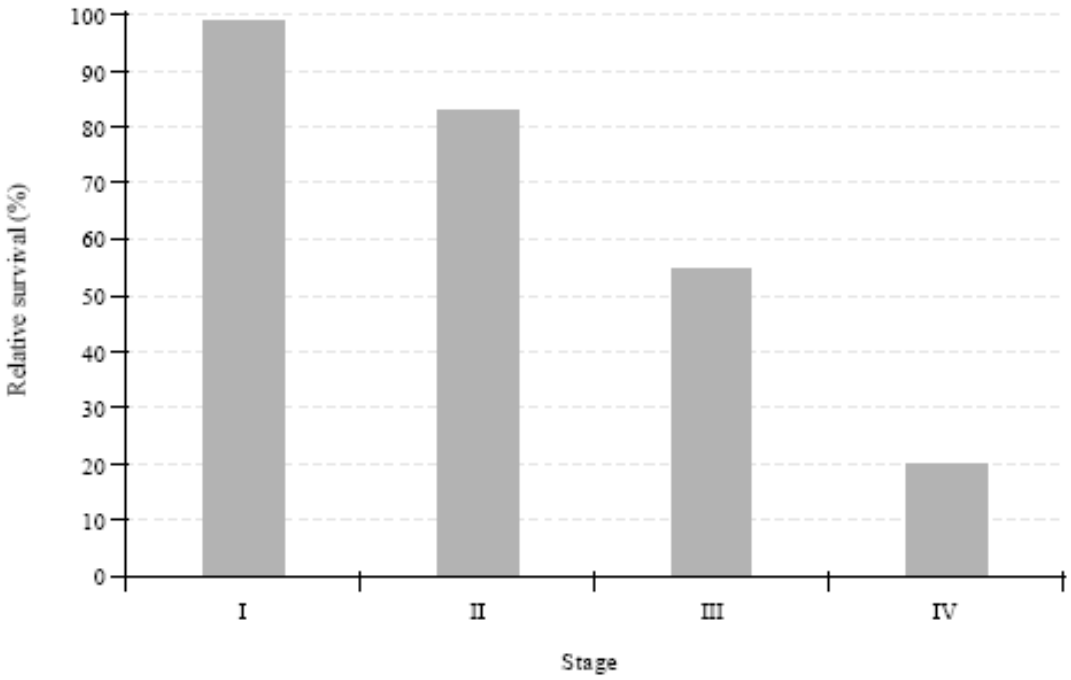
Table 2: Cancers Identified by the Ontario Breast Screening Program (1988-1991 data)

Stage	Percentages of Cancers Identified
I	39.1%
II	38.5%
III	8.6%
IV	10.1%
Unknown	3.6%

Source: Chiarelli, et al.; (2)

The United-States based SEER data provides an approximation of survival estimates as shown in Figure 1 which are probably generalizable to Ontario.

Figure 1: Five-Year Relative Survival, by Stage, for US SEER1 Breast Cancer Cases, 1990-1991



Source: Chiarelli AM, Theis B, Holowaty E, Moravan V,N ishri ED . Breast cancer in Ontario. 1971-1996. Preface/highlights/background [report on the Internet]. October 2000. Cancer Care Ontario. [cited 2007 May 6]. Available at: http://www.cancercare.on.ca/documents/BreastCancerinOntario.pdf

Diagnosis of Breast Cancer

The diagnosis of breast cancer typically begins with physical examination, XMM and US. These preliminary examinations may be followed by FNA or a core needle biopsy after which the patient proceeds to lumpectomy or mastectomy with axillary node dissection if the FNA or core biopsies are positive. Additional examinations are undertaken to assess distant metastases as appropriate. These steps provide staging information, for the purpose of establishing prognosis and treatment plans.

Existing Treatments Other Than Technology Being Reviewed

Imaging Technologies in Breast Cancer

Imaging technologies play a significant role in the screening of asymptomatic women; the differential diagnosis of symptomatic breast lesions or indeterminate XMM; and in treatment planning and follow-up. These imaging technologies include:

- X-ray techniques:
  - Standard XMM
  - Diagnostic mammography (Compression mammography)
- US techniques

Other Imaging Technologies Currently Under Investigation

- Magnetic Resonance Imaging (MRI)
- Radionuclide techniques
  - Scintigraphic techniques
  - Positron Emission Tomography (PET Scanning)

X-Ray Mammography

Although there is considerable variation in the management of patients with breast cancer, the main methods used for initial screening and early detection of breast cancer are XMM and physical examination. Mammographic findings are based on anatomic changes in the breast and the differentiation between normality and abnormality is achieved by differences in density of normal and abnormal tissues. Standard mammography has a sensitivity in the range of 80 to 90% (in women over the age of 50 years) and is the method of choice in screening asymptomatic women. It is the only reliable technique for detecting microcalcification, and its high sensitivity in detecting cancer in women over the age of 50 (with fatty breast tissues) has resulted in an approximate30% reduction in relative risk of dying from breast cancer among these women.

While XMM has a relatively high sensitivity and a significant impact on the diagnosis of breast cancer in asymptomatic women, the specificity and the positive predictive (PPV) value of XMM are low. Khalkhali et al. (7) have reported that only 15 to 30% of mammographically suspicious lesions that require surgical biopsy prove to be histologically malignant. The PPV for XMM has been reported as low as 20 to 30% (8).

Although XMM has a relatively high sensitivity in the examination of fatty breast tissue in older women, it is not reliable in the assessment of dense breast tissue (9-11) found in approximately 25% of women younger than 50 years of age, or in differentiating scar tissue from a tumor.(12) In dense breasts, the image contrast between normal and cancerous tissue is less, so the detection of cancer is less likely. A

higher exposure is needed to achieve adequate film density but this further reduces the sharpness and quality of the image.

An increase in mammographic density following hormonal replacement therapy (HRT) has been reported in about 25% of the HRT users resulting in an increase in false positive and false negative outcomes. Mammographic changes associated with HRT include generalized increase in density and benign tumors or cysts. Some studies have reported a 7 to 21% reduction in sensitivity and a 12 to 50% reduction in specificity of screening mammography in HRT users. (13)

False negative rates for XMM in patients evaluated following breast surgery or radiotherapy has been reported to be as high as 25 to 45% (14).

In summary, while XMM has a significant impact on the diagnosis of breast cancer in asymptomatic women, it cannot always differentiate benign from malignant tumors. This is especially the case in women with dense breasts, or those who have architectural distortion of their breasts following radiation therapy or surgery, or in those with breast implants.

Impact of False Results on Patients and the Health Care System

The cost impact of applying a test with a low PPV can be significant. For example in the United States, it has been estimated that about one-third of the financial cost of a breast screening program is due to the cost of unnecessary biopsies. Consequently, significant savings may be achieved if unnecessary biopsies can be avoided.

The Ontario Breast Screening program has reported a PPV of 6.4% for the initial screen and 8.4% for rescreens for mammography alone. The PPV value of mammography is highest for those referred by both clinical breast examination and mammography (22.8% for initial screens and 23.5% for rescreens), and lowest for those referred by clinical breast examination alone (0.71% for initial screen and 1.1% for rescreens).

While XMM is appropriate for screening purposes, when used as a diagnostic modality in a population with a high prevalence of disease, it is not a good indicator for cancer detection if used in isolation (15). For this reason, adjunctive modalities are required in this situation. Limitation of XMM in detecting lesions in specific clinical situations has led to the investigation and development of complementary imaging techniques such as SMM, US and MRI.

New Technology Being Reviewed - Scintimammography

Description of the Technique

SMM is a nuclear medicine imaging technique that uses radionuclides and has the ability to image malignant breast tumors. SMM requires the administration of a gamma-ray emitting radiopharmaceutical to the patient, and a camera for imaging the lesion.

Radionuclides

The most commonly used radiopharmaceutical for SMM is TC-99m-methoxy isobutyl isonitrile MIBI (99mTc-sestamibi). Since 1994, 99mTc-sestamibi has been used for breast imaging and results have been reported in large series of patients. The tracer has a half-life of 6 hours and is excreted through the liver and biliary system. The exact mechanism of cellular uptake by cancer cells is not clearly understood. It has been shown that 90% of the isotope is accumulated in the mitochondria of tumor cells. (16)

99mTc-sestamibi can be constantly provided from a molybdenum generator in a nuclear medicine laboratory. Therefore, special delivery from a distribution centre is not required.

Other radionuclides that have been used in SMM are summarized in Appendix 3.

Nuclear Medicine Cameras

After injection of the radionuclide, the isotope begins to decay, and emits gamma rays; a gamma camera can be used to detect isotope distribution in the breast cancer cells. The breast under examination is imaged without compression. Gamma-ray photons are electromagnetic waves similar to optical photons, but have much higher energy and a very short wave length, and require special cameras with a collimation system that selectively absorbs the photons and passes them onto the detector head. A detailed description of the gamma camera assembly and an illustration are shown in Appendices 4 and 5.

The detector head covered by the collimator is made up of a large sodium iodide NaI (T1) scintillation crystal (8 to 12 mm thick) and dozens of photomultiplier tubes. When the gamma ray reaches the NaI (T1) crystal, a burst of scintillation photons is emitted by the scintillation crystal, and the photons are detected by the photomultiplier behind the NaI (T1) crystal.

The collimator of the gamma camera is a honeycomb lead structure made up of an array of tunnels or holes. There are 4 major types of collimators; pinhole, parallel hole, converging hole and diverging hole. The pinhole collimator is used to magnify small objects such as the thyroid, by placing the object close to the pinhole. The parallel hole collimator is widely used. The image size remains the same as the object size. The diverging hole collimators minimize the image and are useful for imaging a large object with a small camera. The converging collimator magnifies the image and is useful for imaging smaller objects.

Planar and SPECT Imaging Techniques

The planar imaging technique is 2-dimensional. Three-dimensional imaging is possible using tomography, the most common technology for this being single photon emission computed tomography (SPECT). The quality of the image depends on the quality and integrity of the camera, the type of collimator, and the positioning of the patient during imaging.
Regulatory Status

According to Health Canada, Miraluma, a brand name for the radiopharmaceutical 99mTc-sestamibi , has been approved for marketing in Canada. It is indicated as a second line diagnostic aid to assist in the evaluation of breast lesions in patients for whom mammography cannot exclude malignancy. According to Health Canada, 99mTc-sestamibi is not indicated for breast cancer screening, to confirm the presence or absence of malignancy, and is not an alternative to biopsy. [Personal communication, Health Canada, 2003]

Nuclear medicine cameras used in Ontario are summarized in Appendix 6.

Literature Review on Effectiveness

Objective

This evaluation addresses the clinical indications for and effectiveness of SMM in the diagnosis of breast cancer.

Questions Asked

What are the clinical indications and effectiveness of SMM in breast cancer detection?

How does SMM compare with US, the routinely used technique? This question will be addressed through an analysis of studies in which SMM, US and XMM are compared and assessed to improve patient selection for biopsy.

What is the evidence for the safety of SMM?

Methods

A structured literature search was conducted to identify human studies in the English language specifically addressing the use of SMM in the diagnosis of primary breast cancer. Potentially eligible studies were identified by searching medical databases for the period between 1992 and October 2002, since the potential use of SMM in breast cancer was discovered in 1992, and the first conducted study was published in 1994.

The 2007 update included English- and French-language health technology assessments and English-language studies published from mid-October 2002 to January 31, 2007. Excluded were case reports, comments, editorials, and letters.

Search Terms

The updated search strategy is detailed in Appendix 1. Search terms included “scintimammography”, “breast neoplasm”, “radionuclide imaging”, “technetium Tc 99mTc-sestamibi”, “methoxy isobutyl isonitrile technetium Tc 99m”, and “ultrasonography”. The citation lists of all relevant articles were also examined to identify other potentially relevant publications to assure complete retrieval of articles.

The following inclusion and exclusion criteria were selected for comparative studies.

Inclusion Criteria

- Studies which compared the diagnostic accuracy of SMM with US in breast cancer diagnosis
- Studies utilizing 99mTc-sestamibi, which has been studied more than the alternative radionuclide agents

- English-language articles, and English and French-language health technology policy assessments. If the same trial was published more than once, the most recently published study was considered.

Exclusion Criteria

- Studies comparing US and SMM as primary screening modalities
- Studies with a sample size of less than 25
- Studies focusing on chemotherapeutic effects
- Studies comparing radioactive pharmaceuticals
- Studies not specific to planar imaging (2-dimensional). For example, studies of SPECT (3-dimensional SMM)

Outcomes of Interest

Selected endpoints for this assessment were the diagnostic values of each technique in terms of sensitivity specificity, accuracy, PPV, negative predictive value (NPV), as well as reported adverse effects for SMM and US.

As a result of a general agreement in all studies, the results of the surgical histopathology was accepted as the "Gold Standard" in the assessment.

Results of Literature Review

Search Outcomes

One researcher reviewed the abstract of each comparative study and determined whether the article met the inclusion criteria. The full texts of eligible studies were reviewed to confirm eligibility and to assess the level of the evidence. Levels of evidence were assigned according to the scale shown in Table 3., An additional designation "g" was added for preliminary reports of studies that have been presented to international scientific meetings.

There were 6 published studies that compared the diagnostic value of SMM to US in the initial Medical Advisory Secretariat review completed in February 2003. Two of these studies included patients with palpable breast tumors, 3 studies included patients with either palpable tumors or indeterminate or suspicious XMM findings, and 1 study compared the 2 techniques in patients with dense breast tissues. In addition, 49 studies investigating the diagnostic accuracy of SMM published between 1994 and 1999 were considered in the overall assessment of the technique.
The literature search for the Medical Advisory Secretariat update completed in April 2007yielded 237 articles. The search was restricted to English-language articles published between mid-October 2002 and January 31, 2007. Excluded were case reports, comments, editorials and letters. There were no comparative studies or any health technology assessments (beyond that presented in the 2003 MAS review) on the diagnostic accuracy of SMM as compared with US, as a second line diagnostic tool for breast cancer following XMM.

Table 3: Levels of Evidence in 2003 Medical Advisory Secretariat Report

Type of Study (Design)	Level of Evidence	Number of Eligible Studies Analyzed
Large randomized controlled trial, Systematic reviews of RCTs	1	
Large randomized controlled trial unpublished but reported to an international scientific meeting	1(g)	
Small randomized controlled trial	2	
Small randomized controlled trial unpublished but reported to an international scientific meeting	2(g)	
Nonrandomized trial with contemporaneous controls	3 a	6
Nonrandomized trial with historical control	3b	
Nonrandomized controlled trial unpublished but reported to an international scientific meeting	3g	
Surveillance (database or register)	4a	
Case series, multi-site	4b	49
Case series, single-site	4c	
Case series unpublished but presented to an international scientific meeting	4g	
TOTAL		55

Safety of Scintimammography

99mTc-sestamibi is approved by Health Canada, and is currently used extensively in myocardial perfusion imaging studies. (17)

Intravenous injection of 99mTc-sestamibi has been associated with very few adverse reactions. According to the product monograph, during clinical trials of cardiac imaging studies, approximately 5 to 10 percent of patients experienced a transient metallic or bitter taste a few seconds after the injection which disappeared within 15-30 seconds. Other minor side effects have been observed, such as flushing, headache, nausea and vomiting, dyspepsia, pruritus, fever, dizziness, fatigue, dyspnea and hypotension.

Toxicity studies performed in different animal species show that acute toxicity of the lyophilized kit was observed only at a dose equivalent to approximately 500 times the maximum human dose.

Descriptive Statistics

Diagnostic Accuracy of Scintimammography

A detailed review by Taillefer (18) tabulated the diagnostic accuracy of 99mTc-sestamibi SMM in studies published between 1994 and 1998. This comprehensive review included 2009 patients from 20 studies. The ratio of palpable to nonpalpable lesions in this review was 2.3. Table 4 summarizes the results of Taillefer's review.

Table 4: Review of Accuracy of Scintimammography

Total average sensitivity	85% (1,029 of 1,218 lesions)
Total average specificity	89% (963 of 1,086 lesions)
Total average accuracy	86% (1,992 of 2,304 lesions)
Total average PPV	89% (1,029 of 1,152 lesions)
Total average NPV	84% (963 of 1,147 lesions)

Source: Taillefer R.; (18)

Diagnostic Accuracy of Scintimammography Compared With Ultrasound and X-Ray Mammography

Six comparative studies were considered as potentially relevant for the assessment. The description of these studies is tabulated in Table 5.

Table 5: Studies Comparing Scintimammography to Ultrasound in the Detection of Breast Cancer When Used for Diagnostic Purposes

Study	Publication year	Number of Patients	Number of Lesions	Prevalence of cancer	Patient population
Lam et al. (19)	1996	48	52	69%	Palpable breast lump (100%)*
Yurdakul et al. (20)	1997	31	31	61%	Palpable breast lump (100%)*
Howarth et al. (21)	1999	117	123	84%	Palpable breast lump (93%) /suspicious mass on XMM†
Klaus et al. (22)	2000	25	33	36%	Palpable breast lump /indeterminate XMM or suspicious findings†
Koukouraki et al. (23)	2001	116	116	74%	Palpable (67%) /non-palpable breast lump†
Wang et al. (24)	2002	32	32	75%	Dense breast*

* Provided a detailed table for individual cases; † Did not provide a detailed table for individual cases.

Table 6: Studies Comparing the Performance of Scintimammography to Ultrasound in the Detection of Breast Cancer When Used for Diagnostic Purposes*

Study	Sensitivity		Specificity		PPV		NPV		Accuracy	
	SMM	US	SMM	US	SMM	US	SMM	US	SMM	US
Lam et al. (19)	97	94	69	75	88	89	92	86	88	88
Yurdakul et al. (20)	100	95	67	67	83	82	100	89	87	84
Howarth et al (21)	84	68	80	65	N/A	N/A	N/A	N/A	84	67
Klaus et al. (22)	92	100	95	48	92	52	95	100	94	67
Koukouraki et al. (23)	93	87	83	87	94	95	81	70	91	87
†Wang et al. (24)	83	92	88	38	95	82	64	60	84	78

*NPV refers to negative predictive value; PPV, positive predictive value; SMM, scintimammography; US, ultrasound.
†Wang et al. examined only patients with dense breasts

As indicated in Table 6, studies by Lam et al. (19) and Yurdakul et al. (20) both included patients with palpable lesions and provided a detailed account for individual cases. The detailed tables show that all

malignant lesions in these 2 studies were detected by SMM apart from 1 small size lesion (0.5 cm), resulting in a sensitivity of 97.2% rather than 100%. However, all other malignant lesions in these 2 studies measured more than 1 cm. Detailed tables also reveal how the results were interpreted. It appears that in the study by Lam et al., (19) 2 US inconclusive readings, which turned out to be malignant, were counted as true positive in favor of US. In other words, the reported sensitivity for US of 100% should have been reported as 94%.

Studies that included patients with highly dense breasts or indeterminate mammograms reported higher specificity for SMM compared with US. Klaus et al. (22) reported a statistically significant specificity for SMM compared with US ($P < 0.01$) and Wang et al. (24) reported a significantly higher specificity for SMM compared with US ($P < 0.05$).

Separate tables (Tables 7 and 8) were constructed based on the mammographic results of the 2 studies to see how frequently US or SMM provided an accurate diagnosis in 2 studies where XMM provided/failed to provide an accurate diagnosis.

Table 7: Performance of Ultrasound and Scintimammography in a Study Where X-Ray Mammography Provided/Failed to Provide an Accurate Diagnosis *†

Imaging technique	XMM differentiated malignant from Benign tumors N=43	XMM failed to differentiate malignant from benign tumors N=1	XMM was Inconclusive N=3
US performance +	41/43 (95.3%)	0/1 (0%)	1/3 (33%)
US performance -	2/43 (4.7%)	1/1 (100%)	2/3 (67%)
SMM performance +	42/43 (97.7%)	0/1 (0%)	1/3 (33%)
SMM performance -	1/43 (2.3%)	1/1 (100%)	2/3 (67%)

*(+) refers to satisfactory performance; (-), unsatisfactory performance; N= number of lesions; SMM, scintimammography; US, ultrasound; XMM, x-ray mammography.
† Study conducted in patients with palpable breast lumps
Source: Lam W., et al.; (19)

Table 8. Performance of Ultrasound and Scintimammography in a Study Where X-Ray Mammography Provided/Failed to Provide an Accurate Diagnosis *†

Imaging technique	XMM differentiated malignant from benign tumors N=24	XMM failed to differentiate malignant from benign tumors N=2	XMM was Inconclusive N=2
US performance +	22/24 (91.7%)	1/2 (50%)	0/2 (0%)
US performance -	2/24 (8.3%)	1/2 (50%)	2/2 (100%)
SMM performance +	23/24 (95.8%)	1/2 (50%)	0/2 (0%)
SMM performance -	1/24 (4.2%)	1/2 (50%)	2/2 (100%)

*(+) refers to satisfactory performance; (-), unsatisfactory performance; N= number of lesions; SMM, scintimammography; US, ultrasound; XMM, x-ray mammography.
† Study conducted in patients with palpable breast lumps
Source: Yurkadul G., et al. (20)

Table 9: Successful Differentiation of Breast Cancer Lesions by Ultrasound and Scintimammography *

Clinical situations	US	SMM
Successful differentiation after XMM differentiated the lesions	93.5%	96.8%
Successful differentiation when XMM failed to differentiate the lesions	25%	25%
Successful differentiation when XMM was inconclusive	15%	15%

*SMM refers to scintimammography; US, ultrasound; XMM, x-ray mammography.

The results presented in Tables 7, 8 and 9 show that where XMM could differentiate the lesion, the results of SMM might be better than US, though the small sample sizes and small differences make these comparisons difficult to interpret. In situations where XMM failed to differentiate the lesions, or was inconclusive, SMM and US had similar results.

Only one study compared SMM and US in detecting breast cancer in a sample of patients with dense breasts. Table 10 is constructed to show the performance of each technique in the detection of cancer in dense breasts.

Table 10: Performance of Ultrasound and Scintimammography in Mammographically Dense Breasts Where X-Ray Mammography Results are Indeterminate*

Imaging technique		XMM was inconclusive N=32
US performance	+	25/32 (78%)
	-	7/32 (22%)
SMM performance	+	27/32 (84.4%)
	-	5/32 (15.6%)

(+) refers to satisfactory performance; (-),unsatisfactory performance; N, number of patients; SMM, scintimammography; US, ultrasound; XMM, x-ray mammography.
Source: Wang H., et al.; (24)

Table 10 shows that SMM performed better than the US in situations where XMM was inconclusive because of mammographically dense breasts.

Firm conclusions cannot be derived from these descriptive statistics, but the limited available data suggests that in palpable malignant tumors larger than 1 cm, SMM has a high sensitivity and performs slightly better than US. Also, in dense breasts, Wang et al. (24) reported higher accuracy and specificity for SMM than US.

Review of method to summarize the accuracy data

The definition of true positive and true negative results varied across studies. For example, it is not known how the investigators categorized inconclusive results. As will be discussed in the next section, the dilemma of different test thresholds, which has been applied by different investigators, can be solved by constructing a Summary Receiver Operating Characteristic (SROC) curve.
Variations in reports of sensitivity and specificity may result from different patient populations as well as the different proportions of small tumors in these studies. Furthermore, the intensity of radiopharmaceutical uptake depends on a variety of factors such as size, location, type and hormonal factors.

Meta-analysis

In order for an adjunctive imaging technology to reduce the requirement for biopsy following XMM, the technology should have a very low probability of false negative results. In diagnostic technology, the threshold for a positive test varies in different studies and a tradeoff between sensitivity and specificity is not well defined. Hence, the full picture of the test accuracy cannot be obtained resulting in uncertainty regarding the value of the diagnostic test. These problems can be resolved through a logistic regression analysis. For this reason, a meta-analysis was conducted using the SROC method developed by Moses et al. (25) through a logistic transformation and linear regression.

The Receiver Operating Characteristic (ROC) curve presents the functioning of any diagnostic test by displaying the relationship between true positive and false positive rates. The logit transformation of sensitivity and specificity are used to form the ROC curve. ROC curves can be used as a tool either to derive the optimum operating point for a test (ROC) or as a tool for conducting a meta-analysis of disparate studies (SROC).

The ROC method requires the estimates of the true positive rate (TPR) and the false positive rate (FPR) to calculate the performance and utility of the test. In this model, TPR is a function of FPR and the model uses an appropriate value for TPR for each value of FPR. By converting the TPR and FPR from each study to their logistic transform and plotting the sum and differences of the logistic transforms, a curve is generated and a linear model fitted. The resulting curve can then be back-transformed to produce the ROC curve. The ideal position of a ROC curve is near the upper left corner, which would indicate a perfect test or a perfect technique in differentiating diseased and nondiseased individuals.

Meta-Analysis of Sensitivity and Specificity of Scintimammography

A total of 49 studies on SMM published between 1994 and 1999 with data on 4,540 breast lesions, were used for meta-analysis to summarize the results of these studies (Table 11).

Table 11. Results of Published Studies on Diagnostic Accuracy of Scintimammography (1994-1999)*

Year	Author	N	Malignant	Benign	Sensitivity	Specificity	PPV	NPV	Accuracy	TP	TN	FP	FN
1999	Tofani (26)	300	218	82	89	83	93	74	87	194	68	14	24
	Buscombe (27)	48	26	22	96	82	86	95	90	25	18	4	1
	Cutrone (28)	68	23	45	96	91	85	98	93	22	41	4	1
	Prats (29)	97	41	56	85	70	74	88	81	35	44	12	6
	Danielson (30)	121	86	35	84	74	89	65	81	72	26	9	14
	Howarth (21)	123	103	20	84	80	96	50	84	87	16	4	16
	Melloul (31)	121	18	103	89	88	57	98	88	16	91	12	2
1998	Cwikla (32)	74	53	21	89	52	84	67	80	47	12	9	6
	Arslan (33)	105	52	53	81	87	86	82	84	42	46	7	10
	Cwikla (34)	19	9	10	89	70	73	88	79	8	7	3	1
	De Vincentis (35)	36	32	4	81	100	100	40	83	26	4	0	6
	Palmedo (36)	253	165	88	61	81	85	52	68	100	71	17	65
	Flanagan (37)	80	21	59	81	81	61	92	81	17	48	11	4
	Mekhmandarov (38)	140	85	55	84	85	90	77	84	71	47	8	14
	Tiling (39)	44	24	20	79	80	83	76	80	19	16	4	5
	Tolmos (40)	70	9	61	56	87	38	93	83	5	53	8	4
	Uriarte (41)	78	41	37	93	47	67	86	72	38	18	19	3
1997	Ambrus (42)	51	40	11	95	73	93	80	90	38	8	3	2
	Becherer (43)	174	52	122	77	87	71	90	84	40	106	16	12
	Buscombe (44)	74	53	21	91	71	89	75	85	48	15	6	5
	Carril (45)	41	22	19	86	58	70	79	73	19	11	8	3
	Chen (46)	63	32	31	78	90	89	80	84	25	28	3	7
	Colella (47)	203	156	47	82	89	96	60	84	128	42	5	28
	Helbich- Planar (48)	75	26	49	62	88	73	81	79	16	43	6	10
	Helbich-SPECT (48)	73	24	49	83	80	67	91	81	20	39	10	4
	Scopinaro (49)	449	355	94	85	90	97	61	86	300	85	9	55
	Tiling (50)	56	33	23	88	83	88	83	86	29	19	4	4
	Alonso (51)	64	25	39	76	90	83	85	84	19	35	4	6
	Chiti (52)	16	16	0	94		100	0	94	15	0	0	1
	De Vincentis (53)	14	8	6	75	100	100	75	86	6	6	0	2

	Khalkhali (7)	164	52	112	92	88	77	96	89	48	98	14	4
	Schillaci (54)	198	126	72	83	90	94	76	86	105	65	7	21
	Sillar (55)	18	15	3	93	33	88	50	83	14	1	2	1
	Sommer (56)	81	33	48	88	92	88	92	90	29	44	4	4
	Yurdakul (20)	31	19	12	100	67	83	100	87	19	8	4	0
1996	Villaneuva-Meyer (57)	66	35	31	83	94	94	83	88	29	29	2	6
	Clifford (58)	148	43	105	84	95	88	93	92	36	100	5	7
	Maffioli (59)	24	14	10	50	90	88	56	67	7	9	1	7
	Palmedo (60)	56	27	29	85	66	70	83	75	23	19	10	4
	Maublant (61)	18	16	2	88	0	88	0	78	14	0	2	2
	Moretti (62)	15	13	2	77	100	100	40	80	10	2	0	3
	Lam (19)	52	36	16	97	79	93	92	92	35	11	5	1
	Yuen Green (63)	21	6	15	83	93	83	93	90	5	14	1	1
1995	Lu (64)	40	11	29	91	83	67	96	85	10	24	5	1
	Khalkhali (65)	106	32	74	94	88	77	97	90	30	65	9	2
	Taillefer (66)	65	47	18	92	94	98	81	92	43	17	1	4
	Maurer (67)	75	27	48	67	90	78	83	81	18	43	5	9
1994	Burak (68)	41	27	14	93	86	93	86	90	25	12	2	2
	Kao (69)	38	32	6	84	100	100	55	87	27	6	0	5
	Khalkhali (70)	153	51	102	92	89	81	96	90	47	91	11	4
	Total/Average	4540	2512	2028	84	81	84	76	84	2101	1721	309	409

*FN refers to false negative; FP false positive; N, number of lesions; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

The average of sensitivity, specificity, PPV, NPV and accuracy for the 49 studies was 84%, 81%, 84%, 76% and 84%, respectively. These values mostly concur with data published by Taillefer (18) with the exception of a lower specificity and NPV in this analysis (81% versus 89% and 76% versus 84% respectively).

A meta-analysis using SROC was conducted to summarize the results of the 49 studies on SMM. The data points of the fitted SROC curve are as per Figure 3. The resulting SROC curve is shown in Figure 2.

Figure 2. Summary Receiver Operating Characteristics Based on 49 Studies (1994-1999)

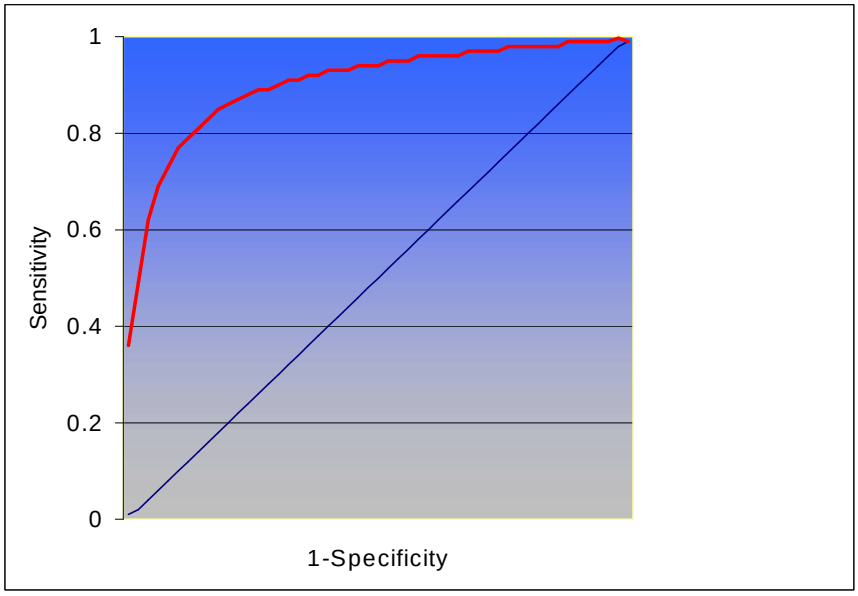
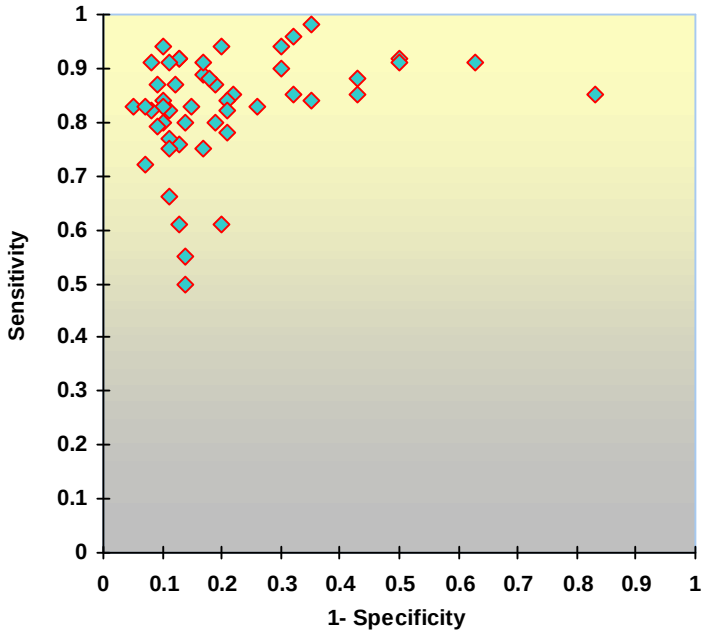


Figure 3. Data Points on the Fitted SROC Curve



Meta-Analysis on Paired Data (SMM Versus US)

Fitting an SROC curve to the data requires information about the test results in a 2×2 table, in a pair of cancer/noncancer individuals. Only 5 comparative studies on SMM and US reported the necessary data and were included for regression analysis. These studies appear in table 12 below.

Table 12: Published Studies Included in Meta-Analysis for Paired Data*

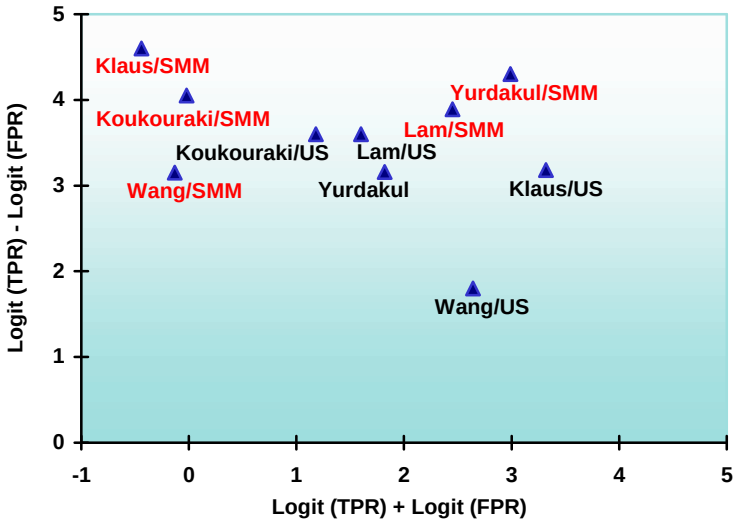
Study	TP		FP		TN		FN		Number
	SMM	US	SMM	US	SMM	US	SMM	US	of lesions
Lam et al.	35	34	5	4	11	12	1	2	52
Yurdakul et al.	19	18	4	4	8	8	0	1	31
Klaus et al.	11	12	1	11	20	10	1	0	33
Koukouraki et al.	80	75	5	4	25	26	6	11	116
Wang et al.	20	22	1	5	7	3	4	2	32

*FP refers to false positive; TN, true negative; TP, true positive; SMM, scintimammography, US, ultrasound.

Overall, 264 lesions in 252 patients were evaluated in these studies.

Figure 4 illustrates the logistic transformation of the TPR and FPR from comparative studies on SMM versus US in differentiating benign and malignant lesions.

Figure 4. Logistic Transformation of the Data



The equation was converted through back-transformation of the regression line to the original unit. The resulting equation is plotted in Figure 5, whereas the data points of this fitted SROC curve for SMM and US are in Figure 6.

Figure 5: Fitted SROC Curves for Differentiation Between Malignant and Benign Breast Lesions Generated From the Data Points of the Five Studies

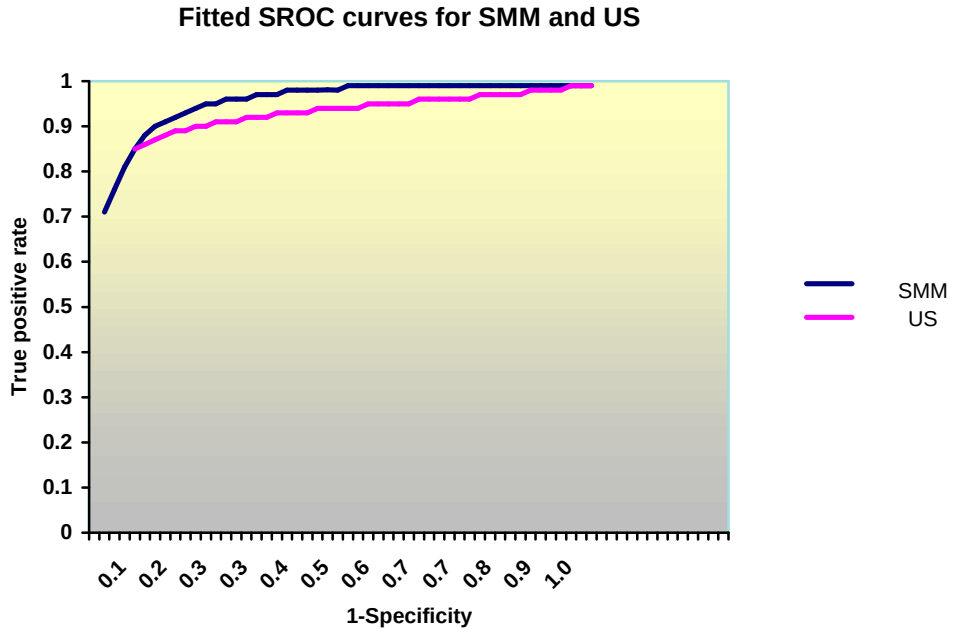
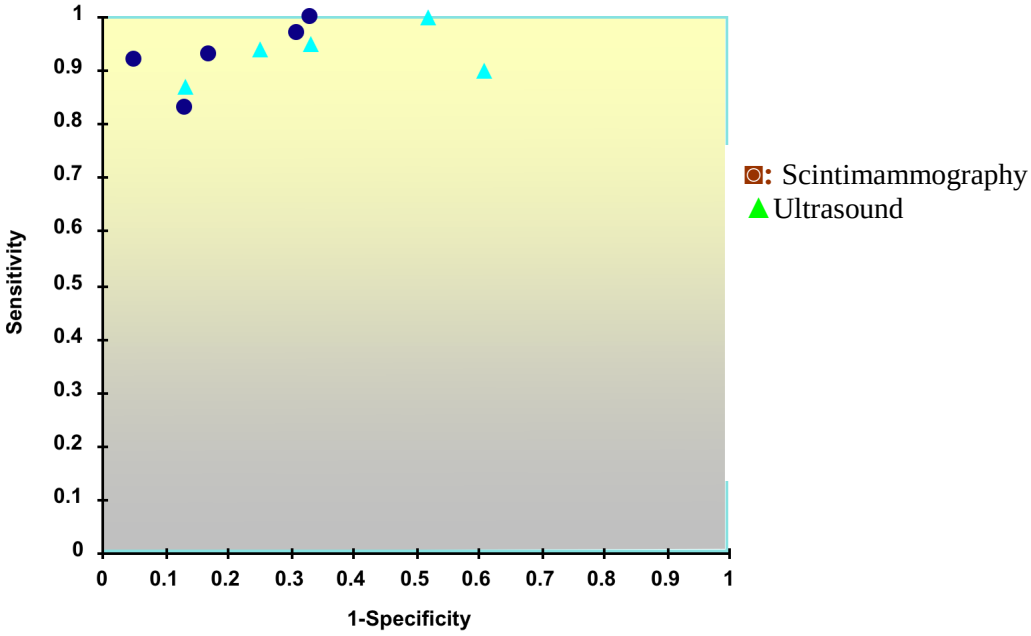


Figure 6. Data Points on the Fitted SROC Curve for Scintimammography and Ultrasound



The resulting SROC curve is the best available summary of studies evaluating the diagnostic accuracy of SMM and US. Through this analytical method, we were able to demonstrate the relationship between TPR and FPR across studies, recognizing that they may have used different thresholds. The SROC curve was not plotted beyond the empirical range of data. Also, an unweighted approach was considered to plot the SROC curve. This approach was adopted according to Moses et al. (25) who recommended the use of unweighted analysis to protect the curve from bias.

Visual inspection of the SROC plot shows little difference between SMM and US. Although the position of the SMM curve is slightly higher than the US curve and the data points are closer to the top left corner of the SROC plot, the area under the curve as a measure of discriminatory power showed minimal difference between the 2 techniques (94% for SMM and 93% for US).

When interpreting this meta-analysis, it must be pointed out that all 5 studies included patients who were both under and over 50 years of age. The generalizability of this analysis to patients under 50 years of age is questionable and warrants a separate analysis. This is especially important since SMM is thought to be more accurate in patients with dense breasts, with scarring or with implants. To clarify this issue, an attempt was made to analyze the data for patients 50 years of age and younger to compare the performance of SMM and US in younger patients. However, three studies provided age information, of which only 2 were eligible to be included in a separate analysis. As a result, a separate analysis was not conducted for younger patients. Should sufficient data become available in future, additional analyses could be performed.

The data accumulated so far, suggests that there may be a role for SMM as an adjunctive technique in the evaluation of breast abnormalities. This role may become clearer once additional data based on newer generation gamma cameras specifically designed to image the breast becomes available.

Brem et al. (71) have reported improved sensitivity for the detection of nonpalpable lesions and lesions smaller than 1 cm with a novel high-resolution breast-specific gamma camera (HRBGC). For nonpalpable lesions, sensitivity was 55.5% with a general purpose camera and 72.2% for HRBGC. For lesions smaller than 1 cm, sensitivity was 47% with a general purpose camera and 67% for HRBGC. The overall sensitivity was reported as 64.3% for the general purpose camera and 78.6% for HRBGC.

Economic Analysis

Notes & Disclaimer

The Medical Advisory Secretariat uses a standardized costing methodology for all of its economic analyses of technologies. The main cost categories and the associated methodology from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative (OCCI) cost data is used for all program costs when there are 10 or more hospital separations, or one-third or more of hospital separations in the ministry's data warehouse are for the designated International Classification of Diseases-10 diagnosis codes and Canadian Classification of Health Interventions procedure codes. Where appropriate, costs are adjusted for hospital-specific or peer-specific effects. In cases where the technology under review falls outside the hospitals that report to the OCCI, PAC-10 weights converted into monetary units are used. Adjustments may need to be made to ensure the relevant case mix group is reflective of the diagnosis and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the Medical Advisory Secretariat normally defaults to considering direct treatment costs only. Historical costs have been adjusted upward by 3% per annum, representing a 5% inflation rate assumption less a 2% implicit expectation of efficiency gains by hospitals.

Nonhospital: These include physician services costs obtained from the Provider Services Branch of the Ontario Ministry of Health and Long-Term Care, device costs from the perspective of local health care institutions, and drug costs from the Ontario Drug Benefit formulary list price.

Discounting: For all cost-effective analyses, discount rates of 5% and 3% are used as per the Canadian Coordinating Office for Health Technology Assessment and the Washington Panel of Cost-Effectiveness, respectively.

Downstream cost savings: All cost avoidance and cost savings are based on assumptions of utilization, care patterns, funding, and other factors. These may or may not be realized by the system or individual institutions.

In cases where a deviation from this standard is used, an explanation has been given as to the reasons, the assumptions and the revised approach.

The economic analysis represents an estimate only, based on assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied for the purpose of developing implementation plans for the technology.

Budget Impact Analysis

- During the fiscal year 2001/2002, a total of 522,844 patients had undergone x-ray mammography in Ontario (Services billed to the Ontario Health Insurance Plan [OHIP] by Ontario physicians [code x185]). In the same fiscal year, a total of 11,363 patients had FNA [code Z141], and a total of 5,990 patients had open biopsy [code R107] billed along with x-ray mammography. The number of patients who had more than one or both services was 2,090 and 3,174 respectively.

Patients billed for FNA [code Z141]	11,363
Patients billed for breast biopsy [code R107]	5,990
Total	17,353

Using figures from OHIP data, a total of 5,264 patients had more than one or both services. Assuming that half of these patients (2,632) had both services multiple times, 14,721 (17,353 - 2,632) women underwent at least one invasive procedure to establish a diagnosis based on an abnormal XMM/US.

It is assumed that all patients who underwent an invasive procedure were candidates for a third line SMM assessment. As a result, approximately 14,721 women will require SMM. This corresponds to the number of women in whom XMM and US were inconclusive, as well as those who were highly suspicious for malignancy and required immediate tissue sampling.

- The exact number of patients with diagnostic XMM who will be directly referred for FNA or biopsy and will not require SMM is not known. This will presumably reduce the number of patients who require SMM.

- The exact number of patients with abnormal XMM and/or US who will require SMM but will not be referred for FNA or biopsy is not known. This will presumably increase the number of patients who require SMM.

- The true percentages of the patients who are candidates for SMM will be dependent on the practice behavior of physicians after the diffusion of the technology in Ontario.

Calculations:

Current fee information regarding estimated fees for administering SMM:

Physician fee: $39.79 Cdn (per Provider Services)
Technical fee: $94.36 Cdn (per Provider Services)

Total: $134.15 (Cdn)

Using 2001/2002 OHIP data as an approximation, the budget impact for adopting SMM in the Province of Ontario would be approximately $2.0 million (Cdn).

Conclusions

Main points from the literature

- An NPV of 98% or greater has been suggested as the acceptable level for any diagnostic test to reliably preclude breast biopsy.

- So far, none of the currently available imaging techniques have achieved this level, and the existence of an overlap between images of malignant and benign lesions requires that a combination of diagnostic tests be used to achieve high levels of accuracy.

- Currently, the diagnostic work-up involves some combination of imaging techniques, as well as invasive procedures for tissue sampling.

- The general agreement among all studies is that XMM represents the only validated imaging technique for screening asymptomatic women.

XMM is less reliable in:

- Detecting lesions in women with mammographically dense breasts
- The evaluation of architectural distortion after surgery or radiation
- Patients with breast implants.
- XMM has a low PPV, resulting in many unnecessary biopsies.
- In the management of breast disease, US is the most frequently used adjunctive technology to XMM

SMM and US are both useful in evaluating dense breasts. Reported advantages of SMM are:

- May play a role in localizing the primary tumor when XMM or US are not contributory. Alternative technologies such as MRI are also being explored in this group of patients.
- The diagnostic accuracy of SMM is not affected by breast density. Once again, alternative technologies such as MRI are also being explored in this group of patients.

Another clinical application of SMM reported in the literature is the investigation of patients with microcalcification. Following the detection of microcalcification, the likelihood of cancer should be investigated and the definite diagnosis in many cases must be obtained by histopathological investigation. SMM can help to make the distinction between malignant and benign calcifications and to decrease the number of unnecessary biopsies.

Common pitfalls for SMM reported in literature are:

- Cannot reliably detect small tumors (< 1 cm).
- Taillefer's (18) review of all studies between 1994 and 1998 shows that no lesion less than 5 mm was detected by the standard detectors which were available at the time the studies were conducted.
- Produces false positive images in younger patients with fibroadenoma and inflammatory lesions.
- Since the sensitivity of SMM is low for lesions smaller than 1 cm, this modality is not recommended for screening purposes.

Results of the Analysis and the Potential Role of SMM

- In the light of the data and meta-regression analysis, it appears that the SMM technique in conjunction with XMM is a promising technique. However, the meta-analysis showed no

convincing difference between SMM and US in differentiating malignant from benign changes.

- While the meta-analysis showed equivalence between US and SMM, there may be a subset of patients for whom SMM could add further benefit. This includes patients in whom XMM and US are inconclusive, and particularly in patients with dense breasts, architectural distortion and implants.

- Combined data from 49 reports on the diagnostic performance of SMM and the related fitted SROC curve to those data, are good evidence that SMM is an effective imaging technique that can improve the ability to classify patients correctly.

- ROC analysis could be used to assess the performance of a wide variety of imaging techniques as well as to explore the efficacy of various combinations of diagnostic tests. The impact of these combinations on the diagnostic outcomes needs to be determined.

- In clinical practice, multiple diagnostic procedures are used in sequence as a basis for a diagnostic decision. Information at each step combined with case history will determine if additional testing is required. Full optimization requires the best sequence of tests, and the best operating point on the ROC curve for each test.

- The data accumulated so far suggests that there may be a role for SMM as an adjunctive technique in the evaluation of breast abnormalities. This role may become clearer once additional data, based on newer generation gamma cameras specifically designed to image the breast, becomes available.

Updated Conclusions

No new comparative evidence on the diagnostic accuracy of SMM and US as a second line diagnostic tool has become available between October 2002 and January 2007. Therefore, the conclusions from the 2003 MAS review remain for this updated version in 2007. The results of the meta-analysis showed that SMM is as effective as US in differentiating benign and malignant breast lesions. However, there may be a role for SMM as a third line adjunctive technique in the evaluation of breast abnormalities, in particular where breast ultrasound examination is inconclusive because of dense breast tissue or architectural distortion resulting from previous surgery or radiation treatment. SMM is thought to be more accurate in patients with dense breasts, and as younger women are more likely to have dense breasts, a separate analysis specific to women under 50 years of age is needed.

Policy Development

Policy Considerations

X-ray mammography is still considered the most effective and efficient screening tool for breast cancer.

SMM is proposed as an adjunctive technology to X-ray mammography in the diagnosis of breast cancer and cannot replace X-ray mammography as a screening tool.

Currently, US is being used as an adjunct to XMM and there is equivalence with SMM. However there are subsets of patients in whom SMM may be more accurate. Alternative technologies for this group of patients includes MRI.

In licensing Miraluma (99mTc-sestamibi) for marketing, Health Canada specifically limits its use as a second line diagnostic aid to assist in the evaluation of breast lesions in whom mammography cannot exclude malignancy. Health Canada further specifies that 99mTc-sestamibi is not indicated for breast screening, to confirm the presence or absence of malignancy, and is not an alternative to biopsy.

As SMM is not indicated to confirm the presence or absence of malignancy, it is not likely to reduce the need for biopsy. Physicians may continue to order a biopsy despite a negative outcome of SMM. Consequently, the technology may produce little advantage in cancer diagnosis or in cost saving.

In the overall comparison, research evidence failed to show significant advantage of SMM over US as a second-line diagnostic tool when XMM could not detect the lesion or was inconclusive. Adding SMM to the general work up of breast cancer would potentially increase the waiting time prior to biopsy.

There is evidence to suggest that SMM may perform better than US as a second line diagnostic tool for a subset of patients who have dense breast, have scarring from radiation or previous surgery or have breast implants. However, this could not be confirmed by statistical analysis of existing data.

SMM probably has not yet reached its full potential. The accuracy of SMM has been found to be less sensitive in detecting small tumours. There is indication that this pitfall may be solved with improvement in the design of gamma cameras suitable for lower energy gamma rays.

Appendices

Appendix 1: Literature Search Strategy

Search date: February 1, 2007
Databases searched: OVID MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cochrane Library, INAHTA (CRD)

Database: Ovid MEDLINE(R) <1996 to January Week 4 2007>
Search Strategy:
---
1 scintimammog$.mp. (291)
2 (breast adj4 scinti$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (183)
3 mammoscinti$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (22)
4 or/1-3 (402)
5 exp Breast Neoplasms/ (70073)
6 exp Technetium Tc 99m Sestamibi/ or sestamibi.mp. or tetrofosmin.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3991)
7 scinti$.mp. or exp Radionuclide Imaging/ [mp=title, original title, abstract, name of substance word, subject heading word] (45974)
8 (miraluma or myoview).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (22)
9 or/6-8 (47012)
10 5 and 9 (1432)
11 4 or 10 (1453)
12 exp Ultrasonography, Mammary/ or echomammogr$.mp. or ultraso$.mp. or sonogra$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (102240)
13 exp Mammography/ or mammogra$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (10943)
14 11 and (12 or 13) (429)
15 limit 14 to (humans and english language) (381)
16 limit 15 to yr="2003 - 2007" (124)
17 15 and (200210: or 200211: or 200212:).ed. (6)
18 16 or 17 (130)
19 limit 18 to (case reports or comment or editorial or letter) (22)
18 not 19 (108)

Database: EMBASE <1980 to 2007 Week 04>
Search Strategy:
---
1 scintimammogra$.mp. or exp SCINTIMAMMOGRAPHY/ (493)
2 (breast adj4 scinti$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (321)
3 mammoscinti$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (21)
4 or/1-3 (693)
5 exp Breast Tumor/ or exp Breast Cancer/ (130973)

6 exp Methoxy Isobutyl Isonitrile Technetium Tc 99m/ (4819)
7 exp TETROFOSMIN TC 99M/ (1180)
8 exp SCINTISCANNING/ (68613)
9 (miraluma or myoview).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (134)
10 5 and (6 or 7 or 8 or 9) (2676)
11 4 or 10 (2783)
12 exp MAMMOGRAPHY/ or mammogr$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (18886)
13 exp Echomammography/ or echomammog$.mp. or ultraso$.mp. or sonogr$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (163209)
14 11 and (12 or 13) (808)
15 limit 14 to (human and english language and yr="2003 - 2007") (227)
16 14 and (200248: or 200249: or 200250: or 200251: or 200252:).ew. (11)
17 15 or 16 (238)
18 limit 17 to (editorial or letter or note) (24)
19 Case Report/ (920771)
20 17 not (18 or 19) (169)

Appendix 2: Method of Evaluation of Diagnostic Tests

Four indices are used to assess the sensitivity, specificity and the accuracy of a diagnostic test. The sensitivity and specificity of a diagnostic test can be assessed by administering the test to one group of persons who have the cancer, and to another group who do not, and then comparing the results. True positives are those who were tested as positive and have the cancer. Those who were tested as negative and do not have the cancer are called true negatives. False positives are those who were tested positive but do not have the cancer and false negatives are those who were tested negative but in fact have the cancer. Sensitivity of a test is determined by the division of the number of true positives by the total number of patients who have the cancer. Specificity is the number of true negatives divided by the number of patients who do not have the cancer. Accuracy is the sum of true positives and true negatives divided by the total number of the patients tested. The PPV of a diagnostic test is determined by the number of true positives divided by all those who were tested as positive. NPV is the number of true negatives divided by all those who were tested as negative.

	Cancer patients	Normal individuals
Tested positive	True + (A)	False + (C)
Tested negative	False - (B)	True - (D)

Sensitivity= A/(A+B); Specificity D/(C+D);
PPV= A/(A+C); NPV= D/(B+D);
Accuracy= (A+D)/(A+B+C+D)

Appendix 3: Radiopharmaceuticals Used in the Detection of Breast Cancer

1	Radiolabeled monoclonal antibodies Anti-CEA, HMFG1, HMFG2, SM3, Tag 72, MoAb-17-OH-82, DF3, BM2 antibodies labeled with ^{131}I, ^{123}I, ^{111}In or ^{99}m Tc
2	Perfusion imaging agents ^{201} T1-chloride ^{99}mTc sestamibi (Cardiolite) ^{99}mTc tetrofosmin (Myoview)
3	Ligands with non-specific uptake ^{99}mTc MDP ^{99}mTc DTPA Others
4	Receptor imaging ^{111}In DTPA-pentetreotide (somatostatin receptors) ^{131}I-E-17 α iodovinyl estradiol (oestrogen receptor) ^{123}I-16 α oestradiol (oestrogen receptors)
5	PET imaging radiopharmaceuticals Glucose metabolism: ^{18}F- fluoro-2-deoxy -D-glucose [FDG] Amino acid metabolism: ^{11}C L-methionine Receptors: 21-^{18}F-fluoro-16 α –ethyl-19-norprogesterone (progestin receptors); 16 α-[^{18}F] –fluoro 17 β-oestradiol (oestrogen receptors)

Source: Gopalan D. et al.; (12)

Appendix 4: Gamma Camera Assembly

The collimator of the gamma camera is a honeycomb lead structure made up of array of tunnels or holes. The length of the septa and the diameter of the holes vary among different gamma camera designs. A collimator with a longer septa and smaller holes defines the photon direction better and produces higher resolution. This design has the disadvantage of lower efficiency, while a collimator with shorter septa and larger holes has higher efficiency but produces lower resolution. Gamma cameras are supplied with a set of different collimators to facilitate adjustments. The collimators therefore play an essential role in imaging quality.

There are 4 major types of collimators; pinhole, parallel hole, converging hole and diverging hole. The pinhole collimator has a small hole usually a few millimeters in diameter at the end of a cone shape apparatus, which can be altered in size. A larger pinhole provides higher efficiency but lower resolution. With this design, the magnification of an object changes with the distance between the object and the pinhole. The magnification effect of the small pinhole collimators is often used to magnify small objects such as the thyroid by placing the object close to the pinhole.

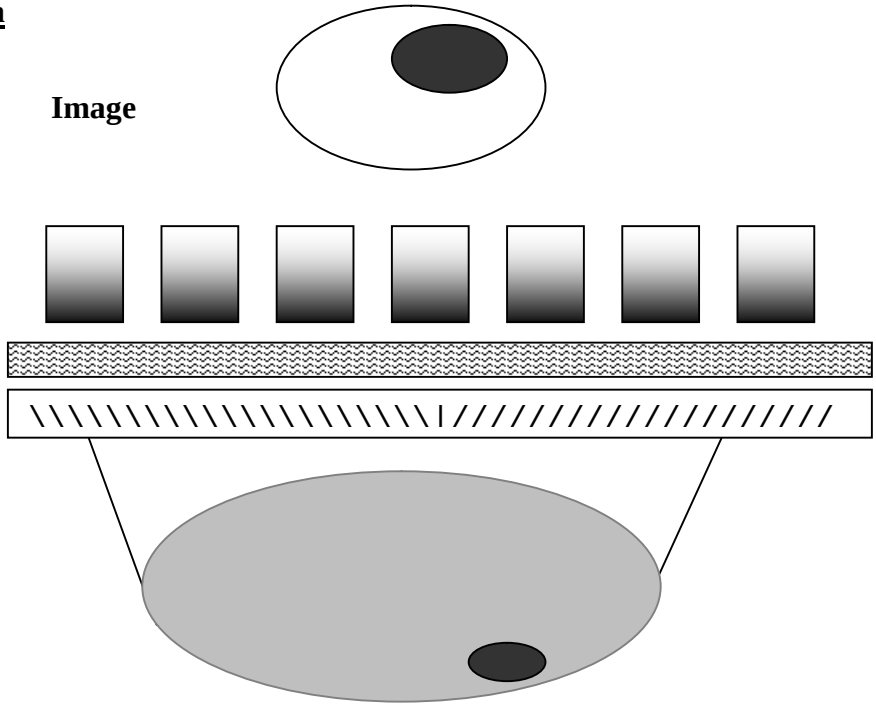
The parallel hole collimator is widely used. The image size remains the same as the object size. The diverging hole collimators minimize the image and is useful for imaging a large object with a small camera. The converging collimator magnifies the image and is useful for imaging smaller objects.

The detector head covered by the collimator is made up of a large sodium iodide NaI (T1) scintillation crystal (8 to 12 mm thick) and dozens of photomultiplier tubes. When the gamma ray reaches the NaI (T1) crystal, a burst of scintillation photons is emitted by the scintillation crystal and the scintillation photons are detected by the photomultiplier behind the NaI (T1) crystal. The NaI (T1) crystal is encapsulated in a sealed canister.

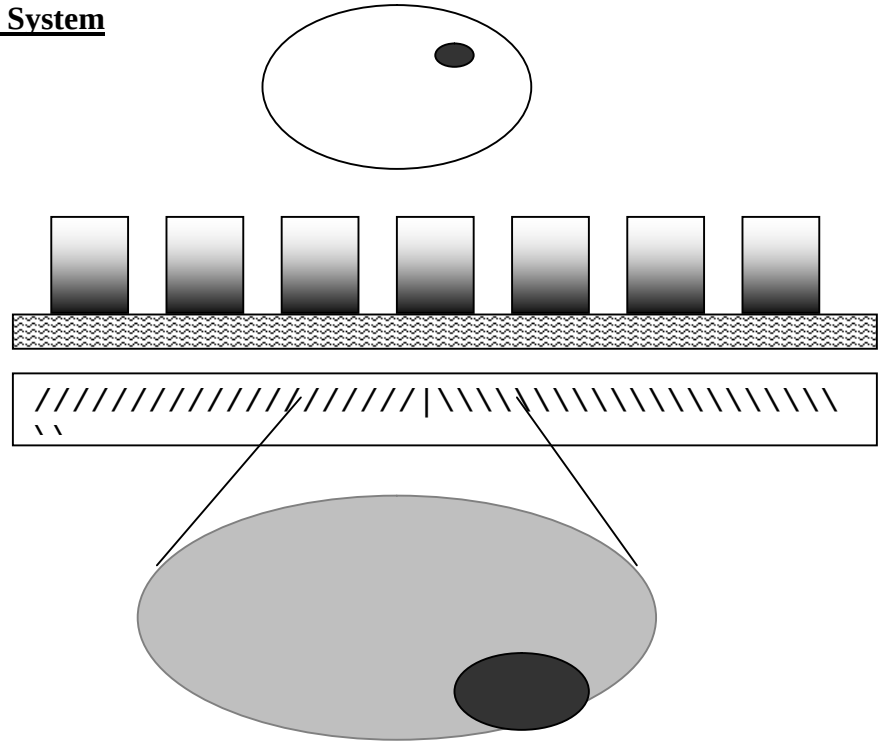
After years of use, if the seal is broken or leaks, the crystal will be damaged, resulting in low quality images. The sealed canister has a glass window that distributes the scintillation lights over the photomultiplier. The thinner crystals (8 mm) provide higher spatial resolution but have lower detection efficiency and are useful for imaging high energy gamma rays such as I^{131}.

Appendix 5: The Assembly of Gamma Cameras

Converging System



Diverging System



Appendix 6: Nuclear Medicine Cameras in Ontario

Region	Hospital	Number of cameras
Central East Region	Lakeridge Health Oshawa	8
	Peterborough Regional Health Centre	2
	South Lake Regional Health Centre	4
	York Central Hospital	4
	Total	14
Central Region Toronto	Hospital for Sick Children	3
	Humber River Regional Hospital- Church St. site	3
	Humber River Regional Hospital- Finch St. site	2
	North York General- Branson Division	3
	North York General- General site	2
	St Michael's Hospital	13
	Sunny Brook & Women's College Hospital	7
	Scarborough Hospital	9
	Toronto East General Hospital	5
	University Health Network	12
	Total	60
Central South Region	Collingwood General & Marine Hospital	1
	General Hospital site Niagara Health System	4
	Greater Niagara General Hospital- Niagara Health System	1
	Hamilton Health Sciences	10
	Hotel Dieu Health Sciences Hospital- Niagara	2
	Orillia Soldiers Memorial	2
	Royal Victoria Hospital	1
	St. Catharines General site- Niagara Health System	1
	Welland Hospital site- Niagara Health System	1
	Total	23
Central West Region	Credit Valley Hospital	2
	Etobicoke Hospital Campus	4
	Joseph Brant Memorial Hospital	2
	St. Mary's General Hospital	5
	William Osler Brampton Campus	3
	Total	16
East Region	Children's Hospital for Eastern Ontario	2
	Cornwall General Hospital	2
	Kingston General Hospital	4
	Ottawa Hospital- Civic Campus	5
	Ottawa Hospital- General Campus	3
	Queensway Carleton Hospital	1
	Quinte Healthcare Prince Country Memorial	3
	University of Ottawa- General Campus	2
	University of Ottawa- Heart Institute	4
	Total	26
North Region	North Bay General Hospital	3
	Sault Area Hospitals	2

	Thunder Bay Regional Hospital	5
	Total	10
South West Region	Bruce-Grey-Owen Sound Health Unit	1
	Lambton Hospitals Group	3
	Leamington District Memorial Hospital	1
	London Health Sciences Centre	10
	St. Joseph Health Care-London	5
	St. Joseph's Hospital- Chatham-Kent Health Alliance	3
	Total	23
	Total number of nuclear cameras in Ontario	172

Source: Canadian Coordinating Office for Health Technology Assessment; (72)

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