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AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary

**Scintimammograms or breast-specific
gamma imaging (BSGI) for the
evaluation of disease spread in women
diagnosed with breast cancer**

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*Adelaide
Health Technology
Assessment*

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PRIORITISING SUMMARY

REGISTER ID: 000441

NAME OF TECHNOLOGY: SCINTIMAMMOGRAMS OR BREAST-SPECIFIC GAMMA IMAGING (BSGI)

PURPOSE AND TARGET GROUP: FOR THE EVALUATION OF DISEASE SPREAD IN WOMEN DIAGNOSED WITH BREAST CANCER

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | | | |
|-------------------------------------|--------------------|--------------------------|------------------------------------------------------------------------|
| <input type="checkbox"/> | Yet to emerge | <input type="checkbox"/> | Established |
| <input type="checkbox"/> | Experimental | <input type="checkbox"/> | Established <i>but</i> changed indication or modification of technique |
| <input checked="" type="checkbox"/> | Investigational | <input type="checkbox"/> | Should be taken out of use |
| <input type="checkbox"/> | Nearly established | | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- Yes
- ARTG number(s): For the gamma camera:
- | | |
|----------------------------------------------------|---------------|
| Philips Electronics Australia Ltd | ARTG #117642 |
| GE Healthcare Australia Pty Ltd | ARTG # 128982 |
| Siemens Ltd | ARTG # 141951 |
| Gammasonics Institute for Medical Research Pty Ltd | ARTG # 167380 |
- No
- Not applicable

Several companies have TGA approved gamma cameras which can be used for the purpose of BSGI, however the BSGI technique does not require approval from the TGA.

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States		✓	

IMPACT SUMMARY:

Several companies, as indicated above, manufacture gamma cameras, however, Dilon Diagnostics[®] (Virginia, USA) actively promote a gamma camera with the aim of providing breast-specific gamma imaging (BSGI), also known as molecular breast imaging (MBI) or scintimammography. The technology would be made available through specialist hospitals for the evaluation of women already diagnosed with breast cancer.

BACKGROUND

BSGI, scintimammography or molecular breast imaging (MBI) has previously been assessed as a potential method for *screening* asymptomatic women in the report “[New and emerging technologies for breast cancer detection](#)”. When used as a diagnostic or screening tool in *asymptomatic*, albeit *high-risk*, women, BSGI had a sensitivity of 76.9 per cent compared to a poor 23.1 per cent for mammography compared to the results of excisional biopsy. In *symptomatic* women, sensitivity was increased to 91.4 per cent when the newer dual-head gamma cameras, as opposed to single-head cameras, were used. This summary seeks to more fully assess the use of BSGI to evaluate women already diagnosed with breast cancer.

BSGI is an invasive procedure first developed in the early 1990s for the diagnosis of cardiac disease. BSGI of the breast uses the radiopharmaceutical and perfusion imaging agent, ^{99m}Tc -sestamibi (^{99m}Tc -sestamibi) (Taillefer 2005). ^{99m}Tc -sestamibi uptake in cancerous cells occurs via the mitochondria, the cytoplasmic organelles responsible for cellular energy production. When used for the diagnosis of heart disease, it was noted that healthy cardiac cells consume more energy and concentrate a greater proportion of the ^{99m}Tc -sestamibi compared to diseased cardiac cells. In cancer, the opposite occurs as diseased, cancerous cells use high levels of energy in comparison and therefore have hyperactive mitochondria. Compared to the healthy surrounding cells, cancerous cells will take up increased levels of ^{99m}Tc -sestamibi and emit more gamma rays, and will show up on the captured images as regions of brightness (Figure 1) (Schmidt 2008).

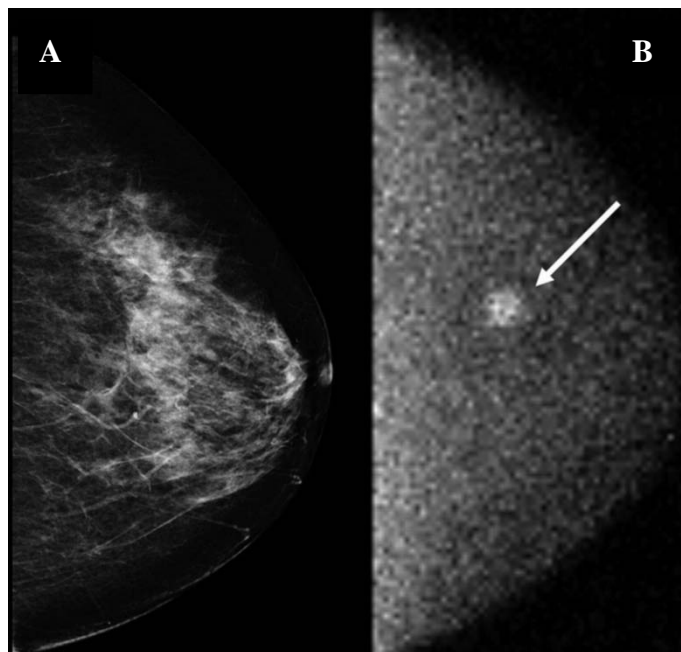


Figure 1 A) Negative image acquired using digital mammography and B) Positive 7mm cancer image acquired with MBI (Schmidt 2008)

The standard dose of ^{99m}Tc -sestamibi used in a BSGI study (740-925 MBq¹), is similar to the dose received in myocardial perfusion studies. Usually the ^{99m}Tc -sestamibi is delivered intravenously as a bolus, however if the patient has a known lesion, the injection should be delivered via the vein in the opposite arm to avoid false positive uptake by the lymph nodes. If bilateral lesions are suspected, the dorsal pedal vein in the foot may be used (Taillefer 2005). A dual-head BSGI system has been developed in which the breast can be positioned between two opposing detectors in a similar fashion as mammography, resulting in improved resolution (Figure 2) (Hruska et al 2008). Images are taken approximately 5-10 minutes after injection and the total time required for examination is 45-60 minutes. BSGI may be of particular use in the detection of breast cancer in women with dense breast tissue and may be used to check for metastases in the axillary lymph nodes or to determine multifocal breast cancers (Prasad & Houserkova 2007).

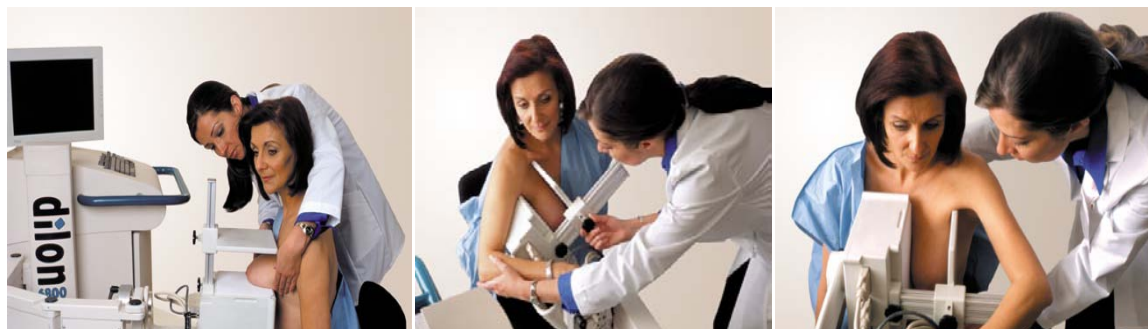


Figure 2 Positioning of the gamma camera in the caudal, oblique and medial views (Dilon Diagnostics 2009)

CLINICAL NEED AND BURDEN OF DISEASE

In Australia, the risk of females developing breast cancer up to the age of 75 years is one in 11 and one in nine up to age 85 years. However, the age-standardised incidence rate is expected to remain relatively the same from 2006-2010 with only a 0.1 projected increase per 100,000 women. In 2005, breast cancer was the most common cancer diagnosed in females with a total of 12,170 cases, accounting for 27.4 per cent of all cancer registrations in women. The age-standardised incidence rate for breast cancer was 110.9 per 100,000 women. In 2005, breast cancer was the second most common cause of cancer death in women with a total of 2,707 deaths, representing a mortality rate of 23.6 per 100,000 women (AIHW and AACR 2008).

In New Zealand, cancer of the breast was the most commonly registered cancer in 2005 with 2,458 registered cases, accounting for 27.4 per cent of all cancer registrations in females. Breast cancer had the highest age-standardised registration rate among females with 92.0 cases per 100,000. In addition, breast cancer was the leading cause of death from cancer among females in 2005, with 648 deaths or 17.1 per cent of all female cancer deaths. Of all cancers, breast cancer had the highest age-

¹ MBq = megabecquerels, a measure of radiation activity

standardised death rate among females with 21.7 deaths per 100,000 (Ministry of Health 2009).

DIFFUSION

Although many specialist hospitals use gamma cameras for other procedures, breast-specific gamma imaging only a few centres in Australia have had limited experience with this technique.

COMPARATORS

Mammography is the gold standard for the diagnosis of breast cancer and both Australia and New Zealand have in place comprehensive population-based mammography screening programs, which target asymptomatic women aged 50-69 years. Masses and calcifications are the most common abnormalities identified on mammograms. The density of a woman's breast tissue will have an effect on the ability of mammography to identify abnormalities, with dense tissue (usually observed on younger women <50 years) reducing the sensitivity of mammography by obscuring abnormalities (Corsetti et al 2008). In cases where mammography may be considered of reduced value, including among women with dense breast tissue, MRI may be indicated (Jones et al 2009). A number of imaging modalities may be used to assess women diagnosed with breast cancer including mammography, MRI and ultrasound.

SAFETY AND EFFECTIVENESS ISSUES

A retrospective review of all women who had undergone BSGI was conducted by Killelea et al (2009) to ascertain its usefulness in the management of women with newly diagnosed breast cancer. A large number of BSGI scans were performed on high-risk women or those with a suspicious mammogram, however 82 scans were completed on women (mean age 53 years, range 33-83) with a biopsy-positive diagnosis of breast cancer. BSGI was compared to other imaging modalities including mammography, ultrasound, positron emission tomography and MRI. As no information was provided in regard to the blinding of imaging and pathology results this study was considered to be level III-2 diagnostic evidence.

Of the 82 BSGI scans performed, 77 detected the presence of a known malignancy (sensitivity 77/82, 94%), however a false negative rate of six per cent was reported (5/82). Two and three of the missed tumours were ductal carcinoma in situ and invasive ductal carcinoma, respectively with an average size of 10mm (range 8-12mm). In 18 patients, BSGI identified lesions which were not detected by other imaging modalities. Of these 18 patients, 17 underwent biopsy of the additional lesions, with the remaining patient opting for mastectomy. BSGI resulted in a change in management in these 18 (22%) patients. Eight patients were biopsy negative despite being BSGI positive (false positive 8/82, 10%). BSGI resulted in a change in

surgical management with 10 patients undergoing additional or more extensive surgery to remove the new lesions (Killelea et al 2009).

A similar retrospective review reported on 138 women with biopsy-proven breast cancer who underwent BSGI for pre-operative evaluation. Diagnosis at biopsy was invasive ductal carcinoma (n=69), invasive lobular carcinoma (n=20), ductal carcinoma in situ (n=32) and mixed pathology (n=17). BSGI scans were compared to surgical pathology findings (level III-2 diagnostic evidence).

Of the 138 women scanned, 25 (18.1%) had a positive BSGI in a position remote from the original biopsied lesion. Ten women (7.2%) were false positives. Four of these patients underwent an additional biopsy which was found to be benign, five patients underwent additional ultrasound and one woman had a mastectomy. Of concern is the high number of false negatives (n=14, 10.1%) who had a negative BSGI scan but had residual tumour on surgical examination. However, 15 (10.9%) patients had a positive BSGI scan for a synchronous or more extensive malignancy in the same (n=8) or contra-lateral breast (n=7). The clinical management was changed in all eight women with additional cancer in the same breast with six women undergoing mastectomy, one undergoing neoadjuvant chemotherapy and the remaining women undergoing a combination of mastectomy and neoadjuvant chemotherapy (Zhou et al 2009).

Single and dual-head BSGI systems were used to investigate 100 and 150 women, respectively, with suspicious breast lesions identified by mammography and/or ultrasound (Hruska et al 2008). All women underwent biopsy after MBI was performed and MBI results were compared to pathology results from core needle biopsy or surgical excision (level III-1 diagnostic evidence).

Of the 100 women in the single-head BSGI study, 47 had benign findings and 53 had breast cancer later confirmed at surgery. In these 53 women, 59 tumours were identified by mammography and/or ultrasound. Although BSGI identified eight tumours in seven patients not detected by mammography, it gave false negative results for 10 tumours in seven patients (sensitivity 57/67, 85%). Possible reasons for the false negative results included five patients with small tumours (<5mm). In addition, all seven patients had large breasts and technical problems, including poor patient positioning (n=5) and low ^{99m}Tc-sestamibi uptake (n=5) may have had an impact on results.

In the dual-head BSGI study, 62 of the 150 women were benign for breast cancer. A total of 128 tumours were detected in the 88 women found to have breast cancer. Of these, 119 were identified with mammography or ultrasound and a further nine were detected with BSGI. The dual-head detector was more sensitive (91%) than the single-head, identifying 117 of the 128 tumours with eleven false negatives reported.

The sensitivity of BSGI according to tumour size using the single or dual head is summarised in Table 1. MBI had the greatest sensitivity for detecting larger tumours

(>10mm), however, sensitivity was greatly improved for the detection of smaller tumours (<10mm) when a dual-head detector was employed.

Table 1 Sensitivity of BSGI according to tumour size

Tumour size (mm)	Single-head MBI	Dual-head MBI
0-5	29% (2/7)	69% (11/16)
6-10	86% (24/28)	91% (41/45)
>10	97% (31/32)	97% (65/67)
All tumours	85% (57/67)	91% (117/128)

The sensitivity of BSGI according to tumour pathology is summarised in Table 2. The dual-head is again more sensitive for the detection of all tumour types.

Table 2 Sensitivity of BSGI according to pathology

Histology	Single-head MBI	Dual-head MBI
Invasive ductal carcinoma (ICD)	84% (37/44)	91% (41/45)
Invasive lobular carcinoma (ILC)	71% (5/7)	81% (17/21)
Ductal carcinoma in situ (DCIS)	100% (8/8)	94% (16/17)
IDC + DCIS	67% (2/3)	100% (29/29)
Mixed IDC + ILC	100% (4/4)	91% (10/11)
Other subtypes	100% (1/1)	80% (4/5)

A small, cross-comparative study (n=26) of women with biopsy proven invasive lobular carcinoma compared the ability of mammography and BSGI to evaluate the extent of disease (Brem et al 2009). The type of head used for the BSGI was not stated, however due to the novelty of using a dual-head it may be assumed that a single-head detector was used in this study. MRI and sonography were also used in some cases. Imaging results were compared to final surgical pathology results. As no information was provided in regard to the blinding of imaging and pathology results this study was considered to be level III-2 diagnostic evidence.

Imaging results for the various modalities are summarised in Table 3. BSGI was the most sensitive imaging modality, detecting 26 of the 28 lesions. The size of lesion detected by BSGI ranged from 2-77mm, with an average size of 20.3mm. The two lesions missed by BSGI measured five and 90mm. BSGI identified six lesions that were occult on mammograms.

Lobular invasive carcinoma represents approximately 10 per cent of all breast cancers but is difficult to detect. This study demonstrates that BSGI may be useful in the evaluation of women with an indeterminate number of lesions.

Table 3 Imaging results for women with invasive lobular carcinoma

Imaging technique	Number of lesions imaged	Image findings		Sensitivity [95% CI]
		Positive	Negative	
MBI	28	26	2	93% [76.5, 99.1]
Mammography	28	22	6	79% [59.1, 91.7]
Sonography	25	17	8	68% [46.5, 85.1]
MRI	12	10	2	83% [51.6, 97.9]

MBI appears to be an effective adjunctive tool for the evaluation of the extent of breast cancer and may be useful in treatment planning of women already diagnosed with breast cancer.

COST IMPACT

The price of a gamma camera is approximately A\$400-500,000 depending on the number of inclusions (personal communication Gammasonics, Australia).

The MBS does not list any item numbers which use ^{99m}Techetium-sestamibi, however several item numbers exist which utilise labelled technetium:

- Item number 61433, whole body study using cells labelled with technetium, fee \$496.95;
- Item number 61434, whole body study using cells labelled with technetium, with single photon emission tomography, fee \$615.40;
- Item number 61441, bone marrow study, whole body study using technetium labelled bone marrow agents, fee \$489.70;
- Item number 61445, bone marrow study, localised using technetium labelled agent, fee \$286.80;
- Item number 61454, localised study using cells labelled with technetium, fee \$348.10;
- Item number 61457, localised study using cells labelled with technetium, with single photon emission tomography, fee \$470.45.

^{99m}Techetium-sestamibi is also used in myocardial perfusion studies (MBS item numbers 61302, 61303, 6106 & 6107) with fees ranging from \$448.85 to \$834.90 (Medicare Benefits Schedule 2009).

Currently sestamibi is manufactured locally in Australia as a “cold kit” and the ^{99m}Techetium is added when required. A typical order would be for 2 GBq which would cost approximately A\$95 (personal communication, Lantheus Medical Imaging Pharmacy).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

As MBI is invasive and uses radiopharmaceuticals, it would not be suitable for use in pregnant women.

MBI may be useful as a post-treatment assessment tool in women diagnosed with breast cancer.

SUMMARY OF FINDINGS

The included studies indicate that BSGI is a useful adjunct in the pre-surgical evaluation of women with biopsy-proven breast cancer. A number of studies indicated changes in clinical management of some women. However, BSGI should be used with caution and in conjunction with other imaging modalities as the number of false negatives and false positives may have serious consequences. As the dual-head camera offers superior imaging for breast lesions of all sizes, the single-head camera should not be considered for the evaluation of women with breast cancer.

HEALTHPACT ACTION:

Based on the evidence available BSGI appears to be useful in the pre-surgical evaluation of women with biopsy-proven breast cancer when used as an adjunct with other imaging modalities including mammography, ultrasound and MRI. Therefore HealthPACT have recommended that a Horizon Scanning Report be commissioned.

NUMBER OF INCLUDED STUDIES

Total number of studies	4
Level III-1 diagnostic evidence	1
Level III-2 diagnostic evidence	3

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SEARCH CRITERIA TO BE USED:

Breast Neoplasms/*radionuclide imaging

*Gamma Cameras

Radiation Dosage

Radiopharmaceuticals/diagnostic use

Sensitivity and Specificity

Technetium Tc ^{99m} Sestamibi/diagnostic use

Neoplasm Invasiveness