

Protocol

Scintimammography and Gamma Imaging of the Breast and Axilla

(60118)

Medical Benefit		Effective Date: 01/01/17	Next Review Date: 11/19
Preauthorization	No	Review Dates: 05/10, 05/11, 05/12, 05/13, 05/14, 05/15, 05/16, 11/16, 11/17, 11/18	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> • With dense breasts or high risk for breast cancer 	Interventions of interest are: <ul style="list-style-type: none"> • Scintimammography, breast-specific gamma imaging and molecular breast imaging as an adjunct to mammography 	Comparators of interest are: <ul style="list-style-type: none"> • Mammography only • Ultrasonography • Magnetic resonance imaging 	Relevant outcomes include: <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Test validity • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With indeterminate or suspicious breast lesions 	Interventions of interest are: <ul style="list-style-type: none"> • Scintimammography, breast-specific gamma imaging and molecular breast imaging 	Comparators of interest are: <ul style="list-style-type: none"> • Mammographic spot compression views • Ultrasonography • Magnetic resonance imaging 	Relevant outcomes include: <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Test validity • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With breast cancer undergoing detection of residual tumor after neoadjuvant therapy 	Interventions of interest are: <ul style="list-style-type: none"> • Scintimammography and breast-specific gamma imaging 	Comparators of interest are: <ul style="list-style-type: none"> • Magnetic resonance imaging • Fluorine 18 fluorodeoxyglucose positron emission tomography • Ultrasonography 	Relevant outcomes include: <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Test validity • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With breast cancer undergoing surgical planning for breast-conserving therapy 	Interventions of interest are: <ul style="list-style-type: none"> • Scintimammography and breast-specific gamma imaging 	Comparators of interest are: <ul style="list-style-type: none"> • Magnetic resonance imaging 	Relevant outcomes include: <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Test validity • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> • With breast cancer undergoing detection of axillary metastases 	Interventions of interest are: <ul style="list-style-type: none"> • Scintimammography and breast-specific gamma imaging 	Comparators of interest are: <ul style="list-style-type: none"> • Surgical nodal dissection 	Relevant outcomes include: <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Test validity • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With breast cancer undergoing sentinel lymph node biopsy for detection of axillary metastases 	Interventions of interest are: <ul style="list-style-type: none"> • Radiopharmaceutical and gamma detection for localization of sentinel lymph nodes 	Comparators of interest are: <ul style="list-style-type: none"> • Localization of sentinel lymph nodes without radiopharmaceutical and gamma detection 	Relevant outcomes include: <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Test validity • Treatment-related morbidity

DESCRIPTION

Scintimammography, breast-specific gamma imaging (BSGI), and molecular breast imaging (MBI) use radiotracers with nuclear medicine imaging as a diagnostic tool for abnormalities of the breast. These tests are distinguished by the use of differing gamma camera technology, which may improve diagnostic performance for detecting small lesions. BSGI uses a single-head breast-specific gamma camera and a compression device; whereas, MBI uses dual-head breast-specific gamma cameras that also produce breast compression. Preoperative lymphoscintigraphy and/or intraoperative hand-held gamma detection of sentinel lymph nodes is a method of identifying sentinel lymph nodes for biopsy after radiotracer injection. Surgical removal of one or more sentinel lymph nodes is an alternative to full axillary lymph node dissection for staging evaluation and management of breast cancer.

SUMMARY OF EVIDENCE

SCINTIMAMMOGRAPHY, BSGI, AND MBI FOR DIAGNOSIS

For individuals who have dense breasts or high risk for breast cancer who receive scintimammography, BSGI, or MBI as an adjunct to mammography, the evidence includes diagnostic accuracy studies. Relevant outcomes are overall survival, disease-specific survival, test validity, and treatment-related morbidity. Three prospective studies have assessed the incremental difference in diagnostic accuracy when BSGI or MBI is added to mammography in women at increased risk. Sensitivity was higher with combined BSGI or MBI and mammography, but specificity was lower. Studies of women at increased risk of breast cancer and negative mammograms found that a small number of additional cancers were detected, but the recall rate was relatively high. Studies tended to include women at different risk levels (e.g., women with dense breasts and those with BRCA1). Moreover, any potential benefits need to be weighed against the potential risks of additional radiation exposure. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have indeterminate or suspicious breast lesions who receive scintimammography, BSGI, or MBI, the evidence includes diagnostic accuracy studies. Relevant outcomes are overall survival, disease-specific survival, test validity, and treatment-related morbidity. In the available studies, compared with biopsy, the negative predictive value of BSGI (or MBI) varied from 83% to 94%. Given the relative ease and diagnostic accuracy of the criterion standard of biopsy, coupled with the adverse consequences of missing a breast cancer, the negative predictive value of BSGI (or MBI) would have to be extremely high to alter treatment decisions. The evidence to date does not demonstrate this level of negative predictive value. Moreover, the value of BSGI in evaluating indeterminate or suspicious lesions must be compared with other modalities that would be used, such as

spot views for diagnostic mammography. The evidence is insufficient to determine the effects of the technology on health outcomes.

SCINTIMAMMOGRAPHY AND BSGI FOR TREATMENT

For individuals who have breast cancer undergoing detection of residual tumor after neoadjuvant therapy who receive scintimammography and BSGI, the evidence includes diagnostic accuracy studies and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, test validity, and treatment-related morbidity. The meta-analysis of studies evaluating the accuracy of BSGI for detecting residual tumor after neoadjuvant therapy found a pooled sensitivity of 86% and a pooled specificity of 69%, compared with histopathologic analysis. No studies were identified that compared the diagnostic accuracy of BSGI with other imaging approaches, or that investigated the clinical utility of this potential application of BSGI. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have breast cancer undergoing surgical planning for breast-conserving therapy who receive scintimammography and BSGI, the evidence includes a retrospective observational study. Relevant outcomes are overall survival, disease-specific survival, test validity, and treatment-related morbidity. In the retrospective study, results suggested that magnetic resonance imaging identified more patients than BSGI who were not appropriate candidates for breast-conserving therapy. Prospective comparative studies are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have breast cancer undergoing detection of axillary metastases who receive scintimammography and BSGI, the evidence includes diagnostic accuracy studies and systematic reviews of diagnostic accuracy studies. Relevant outcomes are overall survival, disease-specific survival, test validity, and treatment-related morbidity. A meta-analysis of the available diagnostic accuracy studies found that the sensitivity and specificity of BSGI are not high enough for this technology to replace the current standard practice, surgical nodal dissection. The evidence is insufficient to determine the effects of the technology on health outcomes.

RADIOPHARMACEUTICAL AND GAMMA DETECTION FOR TREATMENT

For individuals who have breast cancer undergoing sentinel lymph node biopsy for detection of axillary metastases who receive radiopharmaceutical and gamma detection for localization of sentinel lymph nodes, the evidence includes three studies and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, test validity, and treatment-related morbidity. A meta-analysis and three additional studies have provided evidence that using radiopharmaceutical and gamma detection for localization of sentinel lymph nodes yields high success rates in identifying sentinel lymph nodes; additionally, the diagnostic performance generally offers better detection rates with radiopharmaceutical than with alternative methods (e.g., using only blue dye). The evidence has indicated that sentinel lymph node biopsy provides similar long-term outcomes as full axillary lymph node dissection for control of breast cancer and offers more favorable early results with reduced arm swelling and better quality of life. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

POLICY

Scintimammography, breast-specific gamma imaging, and molecular breast imaging are considered **investigational** in all applications, including but not limited to their use as an adjunct to mammography or in staging the axillary lymph nodes.

Use of gamma detection following radiopharmaceutical administration for localization of sentinel lymph nodes in patients with breast cancer may be considered **medically necessary**.

POLICY GUIDELINES

The most commonly-used radiopharmaceutical in BSGI or MBI is technetium 99m (Tc-99m) sestamibi.

The 2013 Breast Imaging Reporting and Data System (BI-RADS) breast assessment and breast tissue categories are summarized in Table PG1.

Table PG1. 2013 BI-RADS Breast Assessment and Breast Tissue Categories

Grading Schema	Category
Assessment categories	
	Incomplete
1	Negative
2	Benign
3	Probably benign
4	Suspicious
5	Highly suggestive of malignancy
6	Known biopsy-proven malignancy
Breast tissue categories	
a	Breasts are almost entirely fatty
b	Scattered areas of fibroglandular density
c	Heterogeneously dense
d	Extremely dense

Source:

<http://www.acr.org/~media/ACR/Documents/PDF/QualitySafety/Resources/BIRADS/01%20Mammography/02%20%20BIRADS%20Mammography%20Reporting.pdf>.

BI-RADS: Breast Imaging Reporting and Data System.

The most commonly used radiopharmaceuticals for sentinel lymph node detection using either lymphoscintigraphy or hand-held gamma detection include Tc 99m-labeled colloids (e.g., sulfur colloid).

BACKGROUND

MAMMOGRAPHY

Mammography is the main screening modality for breast cancer, despite its limitations in terms of less than ideal sensitivity and specificity. Limitations of mammography are a particular issue for women at high risk of breast cancer, for whom cancer risk exceeds the inconvenience of more frequent screening, starting at a younger age, with more frequent false-positive results. Furthermore, the sensitivity of mammography is lower in women with radiographically dense breasts, which is more common among younger women. The clinical utility of adjunctive screening tests is primarily in the evaluation of women with inconclusive results on mammography. A biopsy is generally performed on a breast lesion if imaging cannot rule out malignancy with certainty. Therefore, adjunctive tests will be most useful in women with inconclusive mammograms if they have a high negative predictive value and can preclude the need for biopsy. Additional imaging for asymptomatic women who have dense breasts and negative mammograms has been suggested, but the best approach is subject to debate (see the TEC Special Report [2013]¹).

SCINTIMAMMOGRAPHY

Scintimammography is a diagnostic modality using radiopharmaceuticals to detect breast tumors. After intravenous injection of a radiopharmaceutical, the breast is evaluated using planar imaging. Scintimammography is performed with the patient lying prone, and the camera positioned laterally, which increases the distance between the breast and the camera. Special camera positioning to include the axilla may be included when the area of interest is an evaluation for axillary metastases.

Scintimammography using conventional imaging modalities has relatively poor sensitivity in detecting smaller lesions (e.g., <15 mm), because of the relatively poor resolution of conventional gamma cameras in imaging the breast.

BREAST-SPECIFIC GAMMA IMAGING

Breast-specific gamma imaging (BSGI) and molecular breast imaging (MBI) were developed to address the poor resolution of conventional gamma cameras. Breast-specific gamma cameras acquire images while the patient is seated in a position similar to that in mammography and the breast is lightly compressed. Detector heads are immediately next to the breast, increasing resolution, and images can be compared with mammographic images. BSGI and MBI differ primarily in the number and type of detectors used (e.g., multicrystal arrays of cesium iodide or sodium iodide, or nonscintillating, semiconductor materials, such as cadmium zinc telluride). In some configurations, a detector is placed on each side of the breast and used to compress it lightly. The maximum distance between the detector and the breast is therefore from the surface to the midpoint of the breast. The radiotracer typically used is technetium 99m (Tc 99m) sestamibi, and MBI takes approximately 40 minutes.²

LYMPHOSCINTIGRAPHY AND HAND-HELD GAMMA DETECTION

Preoperative lymphoscintigraphy and/or intraoperative hand-held gamma detection of sentinel lymph nodes is a method of identifying sentinel lymph nodes for biopsy after radiotracer injection. Surgical removal of one or more sentinel lymph nodes is an alternative to full axillary lymph node dissection for staging evaluation and management of breast cancer. Several trials have compared outcomes following sentinel lymph node biopsy with axillary lymph node dissection for managing patients who have breast cancer. The National Surgical Adjuvant Breast and Bowel Project trial B-32 examined whether sentinel lymph node dissection provides similar survival and regional control as full axillary lymph node dissection in the surgical staging and management of patients with clinically invasive breast cancer. This multicenter randomized controlled trial included 5611 women and observed statistically similar results for overall survival, disease-free survival, and regional control based on eight-year Kaplan-Meier estimates.³ Additional three year follow-up of morbidity after surgical node dissection revealed lower morbidity in the sentinel lymph node dissection group, including lower rates of arm swelling, numbness, tingling, and fewer early shoulder abduction deficits.⁴ A recent systematic review and meta-analysis by Ram et al (2014) reported no significant difference in overall survival (hazard ratio, 0.94; 95% confidence interval, 0.79 to 1.19), no significant difference in disease-free survival (hazard ratio, 0.83; 95% confidence interval, 0.60 to 1.14), and similar rates of locoregional recurrence.⁵ However, axillary node dissection was associated with significantly greater surgical morbidity (e.g., wound infection, arm swelling, motor neuropathy, numbness) than sentinel node biopsy.

RADIOPHARMACEUTICALS

Scintimammography, BSGI, and MBI

The primary radiopharmaceutical used with BSGI or MBI is Tc 99m sestamibi. The product label states that Tc 99m sestamibi is "indicated for planar imaging as a second-line diagnostic drug after mammography to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass. Technetium Tc-99m sestamibi is not indicated for breast cancer screening, to confirm the presence or absence of malignancy, and it is not an alternative to biopsy."⁶

Technetium TC-99m tetrofosmin (Myoview™), a gamma-emitter used in some BSGI studies,^{7,8} is approved by the Food and Drug Administration (FDA) only for cardiac imaging.⁹

Lymphoscintigraphy and/or Hand-Held Gamma Detection

The primary radiopharmaceuticals used for lymphoscintigraphy include Tc 99m pertechnetate-labeled colloids and Tc 99m tilmanocept (Lymphoseek).¹⁰ Whereas, Tc 99m sulfur colloid may frequently be used for intraoperative injection and detection of sentinel lymph nodes using hand-held gamma detection probe.

RADIATION EXPOSURE

Scintimammography, BSGI, and MBI

The radiation dose associated with BSGI is substantial for diagnostic breast imaging modalities. According to Appropriateness Criteria from American College of Radiology, the radiation dose from BSGI is 10 to 30 mSv, which is 15 to 30 times higher than the dose from a digital mammogram.¹¹ According to the American College of Radiology, at these levels, BSGI is not indicated for breast cancer screening.

According to a study by Hruska and O'Connor (2015; who reported receiving royalties from licensed technologies by an agreement with Mayo Clinic and Gamma Medica), the effective dose from a lower "offlabel" administered dose of 240 to 300 MBq (6.5 to eight mCi) of Tc 99m sestamibi that is made feasible with newer dual-head MBI systems, is two to 2.5 mSv. For comparison, the effective dose (i.e., mean glandular dose) of digital mammography is estimated to be about 0.5 mSv.¹² However, it is important to note that the dose for MBI is given to the entire body. The authors compared this dose with the estimated annual background radiation, which varies worldwide between 2.5 mSv and 10 mSv, and asserted that the effective dose from MBI "is considered safe for use in routine screening."

Hendrick (2010) calculated mean glandular doses and lifetime attributable risks of cancer, due to film mammography, digital mammography, BSGI, and positron emission mammography (PEM).¹³ The author, a consultant to GE Healthcare and a member of the medical advisory boards of Koning (manufacturer of dedicated breast computed tomography) and Bracco (magnetic resonance contrast agents), used group risk estimates from the Biological Effects of Ionizing Radiation VII report¹⁴ to assess the risk of radiation-induced cancer and mortality from breast imaging studies. For a patient with average-sized breasts (compressed thickness during mammography of 5.3 cm per breast), estimated lifetime attributable risks of cancer at age 40 were:

- five per 100,000 for digital mammography (breast cancer only),
- seven per 100,000 for screen-film mammography (breast cancer only),
- 55 to 82 per 100,000 for BSGI (depending on the dose of Tc 99m sestamibi), and
- 75 for 100,000 for PEM.

Corresponding lifetime attributable risks of cancer mortality at age 40 were:

- 1.3 per 100,000 for digital mammography (breast cancer only),
- 1.7 per 100,000 for screen film mammography (breast cancer only),
- 26 to 39 per 100,000 for BSGI, and
- 31 for 100,000 for PEM.

A major difference in the impact of radiation between mammography and BSGI or PEM is that, for mammography, the substantial radiation dose is limited to the breast. With BSGI and PEM, all organs are irradiated, increasing the risks associated with radiation exposure.

Notes: The term molecular breast imaging is used in different ways, sometimes for any type of breast imaging involving molecular imaging, including PEM, and sometimes it is used synonymously with the term breast-specific gamma camera, as used in this protocol.

Use of single-photon emission computed tomography and positron emission tomography of the breast are not addressed in this protocol.

REGULATORY STATUS

Several scintillation (gamma) cameras have been cleared for marketing by the FDA through the 510(k) process for “measuring and imaging the distribution of radionuclides in the human body by means of photon detection.”¹⁵ Examples of gamma cameras used in BSGI are the Dilon 6800® (Dilon Technologies) and single-head configurations of Discovery NM750b (GE Healthcare). Dual-head cameras used in MBI include LumaGEM™ (Gamma Medical) (FDA product code IYX) and Discovery NM750b (GE Healthcare).

Tc-99m sestamibi (marketed by Draxis Specialty Pharmaceuticals, Cardinal Health 14, Mallinckrodt, and Pharmalucence) has been approved by the FDA with the following labeling: “Breast Imaging: Technetium TC 99M Sestamibi is indicated for planar imaging as a second-line diagnostic drug after mammography to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass. Technetium TC 99M Sestamibi is not indicated for breast cancer screening, to confirm the presence or absence of malignancy, and it is not an alternative to biopsy.”

In 2013, Tc 99m tilmanocept (Lymphoseek; Navidea Biopharmaceuticals) was approved by FDA for use in breast cancer and melanoma as a radioactive diagnostic imaging agent to help localize lymph nodes. Technetium-99m-sulfur colloid was approved by the FDA through the new drug application (NDA; GE Healthcare, NDA 017456; Mallinckrodt, NDA 017724) process although these products appear to be marketed no longer. In addition, in 2011, Technetium Tc 99m Sulfur Colloid Kit (Pharmalucence) was approved by the FDA through the NDA process (NDA 017858) for use as an injection to localize lymph nodes in breast cancer patients.

In 2018, the FDA granted approval to Northstar Medical Radioisotopes for its RadioGenix™ System, which produces molybdenum 99, the material used to generate Tc 99m. Previously, molybdenum 99 was only produced from enriched uranium in facilities outside of the United States.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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