BlueCross BlueShield of Alabama

Name of Policy:
Positron Emission Mammography (PEM)

Policy #: 462
Category: Radiology

Latest Review Date: June 2014
Policy Grade: C

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Positron emission mammography (PEM) is a form of positron emission tomography (PET) that uses a high-resolution, mini-camera detection technology for imaging the breast. As with PET, PEM provides functional rather than anatomic information on the breast. PEM has been studied primarily for use in pre-surgical planning and staging; it has also been used to monitor therapy response and breast cancer recurrence.

Positron emission mammography (PEM) is a form of positron emission tomography (PET) that uses a high-resolution, mini-camera detection technology for imaging the breast. As with PET, a radiotracer, usually 18F-fluorodeoxyglucose (FDG) is administered and the camera is used to provide a higher resolution image of a limited section of the body than would be achievable with FDG-PET. Gentle compression is used, and the detector(s) are mounted directly on the compression paddle(s). PEM was developed to overcome the limitations of PET for detecting breast cancer tumors. Patients usually are supine for PET procedures and the breast tissue may spread above the chest wall, making it potentially difficult to differentiate breast lesions from other organs that take up the radiopharmaceutical. PET's resolution is generally limited to about t mm, which may not detect early breast cancer tumors. PEM allows for the detection of lesions smaller than 2 cm, and creates images that are more easily compared to mammography, since they are acquired in the same position. Three-dimensional reconstruction of the PEM images is also possible. As with PET, PEM provides functional rather than anatomic information on the breast. In studies of PEM, exclusion criteria included some patients with diabetes. PET may be used for other indications for breast cancer patients namely, detecting loco-regional or distant recurrence or metabasis (except axillary lymph nodes) when suspicion of disease is high and other imaging is inconclusive.

Policy:

Positron emission mammography (PEM) **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for all indications**.**

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

A literature search using MEDLINE was performed through May 2014, using the terms ((positron emission mammography) or PEM) and breast. The most recent, highest quality evidence is summarized in this section. No randomized, controlled trials beginning with use of PEM and following up through clinical outcomes were found.

PEM for Use in Women With Newly Diagnosed Breast Cancer as Part of Presurgical Planning

The published literature, comprising two prospective, nonrandomized comparative studies, one prospective, single-arm study, and a meta-analysis that included these studies, is summarized.

Nonrandomized Comparative Studies

At a single site, a prospective study comparing PEM and MRI (1.5 T) was conducted to assist in pre-surgical planning. The performance of PEM, MRI, and whole-body positron emission tomography (WBPET) were compared with final surgical histopathology among 208 women with newly diagnosed, biopsy-proven breast cancer. For PEM and WBPET (performed consecutively), the median FDG dose was 432.9MBq (equivalent to 11.7mCi). Patients' 4-6 hour fasting glucose had to be less than 7.8mmol/L. One of six readers evaluated the PEM, x-ray mammography, and MRI images with access to conventional imaging (mammography or ultrasound) results "but without influence of the alternative (PEM or MRI) imaging modality"; WBPET images were interpreted by a nuclear physician. For evaluating PEM images, readers used a proposed PEM lexicon based on MRI BI-RADS. Patients underwent surgery about three weeks after PEM and WBPET imaging. There were 182 malignant index lesions (45.6% clinically palpable), and 67 additional ipsilateral lesions. Of 250 patients approached to participate in this study, 239 enrolled, 31 were disqualified, and 26 were ineligible because they underwent PEM or MRI before study entry; the analysis therefore includes 182 patients. Almost half (45.6%) of lesions were clinically palpable. On pathology, 77.5% of patients had invasive disease; 20.9% DCIS; and 1.6% Paget's disease. For index lesions, both PEM and MRI have a sensitivity of 92.8% (95% confidence interval [CI]: 88%, 96%; p=not significant [NS] between tests), which was greater than the WBPET sensitivity of 67.9% (95% CI: 60%, 70%; p<0.001). The specificity was not reported since only malignant index lesions were analyzed. The sensitivity of PEM and MRI were not affected by breast density, menopausal status, or use of hormone replacement therapy. PEM tended to overestimate the size of the largest lesion, compared to surgical pathology and MRI (120mm for PEM vs. 95mm for pathology and MRI); however, the Spearman's correlation coefficient between size on histopathology versus size on either PEM or MRI was the same at 0.61. Twelve lesions were missed on both PEM and MRI; three of them were not in the PEM field of view due to patient positioning. For the 67 additional ipsilateral lesions detected (40 malignancies), the sensitivity of PEM and MRI were 85% (95% CI: 70%, 94%) and 98% (95% CI: 89%, 100%; p=0.074) respectively; and the specificity of PEM and MRI, were 74% (95% CI: 54%, 89%) and 48% (95% CI: 29%, 68%; p=0.096), respectively. Although the differences in sensitivity and specificity between PEM and MRI are not statistically significant, the difference in numerical values is quite large (i.e., 85% vs. 98% and 74% vs. 48%). Further investigation is needed to determine whether these are two points along the same operating curve (i.e., whether PEM is being read to emphasize specificity compared to MRI). Additional, larger studies are also warranted.

The results of a trial comparing PEM and MRI were reported at the 2010 Annual Meeting of the Radiological Society of North American (RSNA) and simultaneously published in the journal *Radiology*. The study was funded in part by Naviscan, which manufacturers the FDA-cleared PEM device, and by the National Institutes of Health. The first author is a consultant to Naviscan; other authors include a former employee and a current employee.

The study was conducted at six sites among 388 women with newly diagnosed breast cancer detected at core-needle or vacuum-assisted biopsy and who were eligible for breast-conserving

surgery. The median age was 58 years. Among 427 women originally enrolled, 18 were ineligible and 66 were excluded. The latter 66 patients were statistically significantly more likely than the women included in the analysis to have larger invasive tumor components, to be less likely to have one ipsilateral malignancy at study entry, and to be more likely to have known axillary node metastases (and more missing data). Among study participants included in the trial, tumor size was limited to 4cm or less or to 5cm for women with large breasts. PEM and MRI were performed in random order without regard to timing in the menstrual cycle. The mean FDG dose used with PEM was 10.9mCi, and the mean blood glucose level was 91g/dL. PEM and MRI were read by different investigators; some but not all readers were blinded to results of the other test. PEM results with a BIRADS score of 4a or higher or a score of 3 with a recommendation for biopsy were considered a positive results. Negative cases included those with negative pathology or follow-up of at least six months with no suspicious change.

Prior to surgery, 404 malignancies were detected in 388 breasts. After surgery, 386 lesion sites in 371 breasts were confirmed. This difference is presumably due to biopsies that removed all malignant tissue. Among the 386 lesion sites confirmed during surgery, there was no statistically significant difference in the sensitivity of PEM (92.5%) and MRI (89.1%) when only tumor sites were included, although the authors state that "PEM tended to better depict cancer when it was present…(p=0.79, nonsignificant difference)." When both tumor and biopsy sites were visualized, MRI had a higher sensitivity than PEM (98.2% vs. 94.5%, respectively; p=0.004). There were no visible tumor or biopsy site changes in seven breasts on MRI and in 19 cases on PEM; however, there was residual tumor on surgery in all of these breasts.

Twenty-one percent of the 388 women had additional foci of tumor after study entry. The sensitivity in identifying breasts with these lesions was 60% (95% CI: 48%, 70%) for MRI and 51% for PEM (95% CI: 40%, 62%; p=0.24). Of the 82 additional lesions, 21 (26%) were detected only with MRI, 14 (17%) only with PEM (p=0.31), and seven (8.5%) only with conventional imaging. Adding PEM to MRI increased the sensitivity from 60% to 72% ($p < 0.01$). Twelve women with additional foci in the breast with the primary tumor were not identified by any of the imaging techniques. Among the women with an index tumor and no additional lesions in the ipsilateral breast, PEM was more specific than MRI (91.2% vs. 86.3%, respectively, p=0.032). There was no statistically significant different between PEM and MRI in accuracy or area under the receiver operating characteristic (ROC) curve. Again, the question arises whether the differences in specificity and sensitivity between the two tests are due to selecting different operating points along the ROC curve.

Of the 116 unknown malignant lesions unknown at study entry, 53% were reported as suspicious on MRI versus 41% on PEM (p=0.04). There is no difference between PEM and MRI in detecting DCIS in this study (41% vs. 39%; p=0.83). Adding PEM to MRI would increase the sensitivity for detecting DCIS from 39% with MRI alone to 57% combined (p=0.001; another seven DCIS foci were seen only on conventional imaging). MRI is more sensitive than PEM in detecting invasive cancer, but the two combined would still have a higher sensitivity than MRI alone (73% vs. 64%, p=0.025). MRI is more sensitive than PEM in dense breasts (57% vs. 37%, respectively, p=0.031.

In a second article based on the same study, the performance of PEM and MRI were compared in detecting lesions in the contralateral breast among the same study population. In this case, readers were blinded to the results of the other test but knew the conventional imaging and pathology results from pre-study biopsies. After recording results for a single modality, the reader then assessed the results across all modalities. The reader had one to 15 years of experience in interpreting contrast-enhanced breast MRI and underwent training in interpreting PEM results; five of the 30 readers had prior experience in interpreting PEM images. The final sample size was 367. Nine patients were excluded because the highest scored lesion was a BIRADS 3 (probably benign) based on all imaging, and no follow-up or histopathology was performed. The contralateral breast could not be assessed in 12 women, e.g., due to prior mastectomy or lumpectomy and radiotherapy.

Fifteen (4.1%) of the 367 participants had contralateral cancer. PEM detected cancer in three of these women and MRI, in 14. The sensitivity of PEM and MRI was 20% (95% CI: 5.3%, 45.8%) and 93% (95% CI: 66%, 94%), both respectively ($p<0.001$), while the specificity was 95.2% (95% CI: 92.2%, 97.0%) and 89.5% (95% CI: 85.7%, 92.4%), both respectively ($p=0.002$). The area under the receiver operating characteristic curve was 68% (95% CI: 54%, 82%) for PEM and 96% (95% CI: 94%, 99%) for MRI ($p<0.0001$). There was no statistically significant differences across modalities in the accuracy or positive predictive value for women undergoing biopsies (21% for PEM vs. 28% for MRI; $p=0.58$). There were more benign biopsies based on MRI results (39 biopsies in 34 of 367 women) than for PEM results (11 biopsies in 11 of 367 women) ($p<0.001$). The authors discussed possible improvements in interpreting PEM, based in part on results of having the lead investigators reread the PEM images. They determined that seven of 12 false-negative PEM results were due to investigator error. This could only be confirmed through further study. They also noted that a substantial proportion of contralateral lesions may be effectively treated by chemotherapy. They also noted that PEM cannot optimally evaluate the extreme posterior breast.

Three of six sites included in the Berg et al study participated in a substudy that compared the diagnostic performance of PEM with that of WBPET and PET/CT in two small cohorts of women with newly diagnosed breast cancer who were eligible for breast conserving surgery. Fasting blood glucose less than 148 mg/dL was required for study entry. Of 388 women in the original study, 178 (46%) participated in the substudy. Use of WBPET or PET/CT was determined by protocols at each participating site. Most patients (113 [63%]) underwent PEM followed by WBPET or PET/CT on the same day with the same radiotracer dose; the remaining 65 patients (37%) had PET/CT a median of three days before PEM (range, 20 days before to seven days after) with a whole body-specific dose of FDG. Sensitivity, specificity, and PPV for cancer detection were similar for PET/CT performed on the same day as PEM (mean FDG dose 411 MBq) or on a different day (mean FDG dose 566 MBq). These subgroups were therefore combined for analysis. Readers interpreting PEM images were blinded to WBPET and PET/CT results but had access to radiographic mammography, ultrasound, and pre-study biopsy results. For any identified lesion, a true positive was defined as diagnosis of malignancy within one year; true negative was defined as diagnosis of benign or high-risk pathology as the most severe finding, a probably benign lesion that decreased in size or resolved at any follow-up, or maximum BIRADS score of two after all imaging (PEM, MRI, radiographic mammography, ultrasound). No statistical adjustment for multiple comparisons was made.

In the WBPET cohort (n=69), PEM detected 61 (92%) of 66 index tumors, and WBPET detected 37 (56%; McNemar test, p<0.001). In the PET/CT cohort (n=109), PEM detected 104 (95%) of 109 index tumors, and PET/CT detected 95 (87%, McNemar test, p=0.029). As shown in Table 1, PEM was statistically more sensitive than WBPET (McNemar test, p=0.014) and PET/CT (McNemar test, p=0.003) for detecting additional ipsilateral malignant tumors, but no statistically significant differences in specificity, PPV, or negative predictive value (NPV) between PEM and WBPET or PET/CT were found. Table 1 also shows sensitivities of imaging modalities by index tumor size. Trends for decreasing sensitivity with decreasing tumor size were statistically significant for both WBPET (Cochran-Armitage test, p<0.001) and PET/CT (Cochran-Armitage test, p=0.004) but not for PEM (Cochran-Armitage test, p=0.15). Samples were small for most of these comparisons. Other test performance characteristics (ie, specificity, PPV, NPV) were not reported by tumor size.

The greatest weakness of this substudy was the choice of comparators. Current clinical practice guidelines do not include PET imaging in the diagnostic workup of newly diagnosed breast lesions nor for postoperative surveillance. Conventional imaging (radiographic mammography, ultrasound, and/or MRI) would have been a more informative comparator.

Table 1. Performance of PEM, WBPET, and PET/CT for Ipsilateral Malignant Tumors in Kalinyak et al (2014)

	PEM	WBPET	PEM	PET/CT
	n=69		n=109	
Sensitivity	0.47[a]	0.07	0.57[b]	0.13
Specificity	0.91	0.96	0.91	0.95
PPV	0.58	0.33	0.62	0.43
NPV	0.86	0.79	0.89	0.80
Sensitivity by size of index tumor[c]				
>2 to ≤5 cm	1.0 (12/12)	0.92 (11/12)	0.96 (25/26)	0.96 (25/26)
>1 to <2 cm	0.93 (26/28)[a]	0.61 (17/28)	0.96 (53/55)	0.89 (49/55)
>0.5 to <1 cm	0.91 (21/23)[a]	0.39 (9/23)	0.96 (22/23)	0.83 (19/23)
>0.1 to ≤0.5 cm	0.67 (2/3)	0 (0/3)	0.80 (4/5)	0.40 (2/5)

PPV, positive predictive value; NPV, negative predictive value; WBPET, whole body positron emission tomography

Statistically significant comparisons are noted.

[a] Statistically significant difference vs WBPET (McNemar test)

[b] Statistically significant difference vs PET/CT (McNemar test)

[c] There were no index tumors >5 cm.

Single-Arm Studies

Caldarella et al conducted a systematic review with meta-analysis of PEM studies in women with newly discovered breast lesions suspicious for malignancy. Literature was searched through January 2013. Eight studies (total N=873) of ten or more patients (range, 16-388) that used histological review as criterion standard, including the three studies described in detail next, were included. Pooled sensitivity and specificity were 85% (95% CI, 83 to 88; I2=74%) and 79% (95% CI, 74 to 83; I2=63%), respectively. Pooled PPVs and NPVs were 92% and 64%,

respectively. Comparator arms were not pooled. Other limitations of the study included substantial statistical heterogeneity in meta-analyses and lack of blinding of both PEM and histopathology readers in individual studies.

In an early four-site clinical study, Tafra et al imaged 94 women who had suspected (n=50) or proven (n=44) breast cancer with PEM. Median dose of FDG was 13 mCi. Median patient age was 57 years, and median tumor size was 22mm on pathology review. Seventy-seven percent of primary lesions were nonpalpable. Median time from injection to imaging was 99 minutes; imaging took ten minutes per image, and median slice thickness was 5.2mm. "Unevaluable" cases were excluded (n not reported). Eight readers had access to mammography and clinical breast examination (CBE) results, as well as clinical information, but no information on surgical planning or outcomes. At least two readers evaluated each case in random order. The performance of PEM in this study is listed next; results are presented in detail to illustrate potential uses of PEM:

- BIRADS 4b, 4c, or 5 (probably malignant) assigned to 39 of 44 (89%) pathologically confirmed breast cancers. Five missed lesions ranged in size from 1 to 10mm, and four were low grade.
- Extensive DCIS predicted in three cases and confirmed to be malignant; they were not detected by other imaging modalities.
- Among 44 patients with proven breast cancer, five incidental benign lesions were correctly classified, and four of five incidental malignant tumors were detected, three of which were not detected with other imaging modalities (not evident whether MRI was performed on these specific patients).
- Correctly detected multifocality in 64% of 31 patients evaluated for it, and correctly predicted its absence in 17 patients.
- Correctly predicted six of eight patients undergoing partial mastectomy who had positive margins and 11 of 11 who had negative margins.

Berg et al published a follow-up study of 77 patients. Patients with Type 1 or Type 2 diabetes were excluded; because FDG is glucose-based, diabetic patients must have well-controlled glucose for the test to work. Median age was 53 years. Of 77 patients, 33 had suspicious findings on core biopsy before PEM, 38 had abnormalities on radiographic mammography, and six had suspicious findings on CBE. Five women had personal histories of breast cancer, one of whom had had reconstructive surgery. Readers had access to mammographic and clinical findings, as it was assumed they would in clinical practice. Median dose of FDG was 12mCi (range, 8.2-21.5). Forty-two of 77 cases were malignant, and two had atypical ductal hyperplasia. Sensitivity and specificity of PEM was 93% and 85%, respectively, for index lesions, and 90% and 86%, respectively, for index and incidental lesions. These values were similar or higher if lesions were clearly benign on conventional imaging. Adding PEM to radiographic mammography and ultrasound (when available) yielded sensitivity and specificity of 98% and 41%, respectively. (Specificity of PEM combined with conventional imaging was lower than PEM alone due to the large number of false positive lesions prompted by conventional imaging.)

Other Indications

No full-length, published studies were identified that addressed other indications for PEM, including management of breast cancer and evaluation for recurrence of breast cancer.

Radiation Dose Associated With PEM

The label-recommended dose of FDG for PEM is 370MBq (10mCi). Hendrick calculated mean glandular doses, and from those, lifetime attributable risk of cancer (LAR) for film mammography, digital mammography, breast-specific gamma imaging (BSGI), and PEM. The author, who is a consultant to GE Healthcare and a member of the medical advisory boards of Koning (which is working on dedicated breast computed tomography [CT]) and Bracco (MR contrast agents), used BEIR VII Group risk estimates to gauge the risks of radiation-induced cancer incidence and mortality from breast imaging studies.

Estimated lifetime attributable risk of cancer for a patient with average-sized compressed breast during mammography of 5.3cm (risks would be higher for larger breasts) for a single breast procedure at age 40 years is:

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

The corresponding lifetime attributable risk (LAR) of cancer mortality at age 40 years is:

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

A major difference in the impact of radiation between mammography, on the one hand, and BSGI or PEM, on the other, is that for mammography, radiation dose is limited to the breast, whereas with BSGI and PEM, all organs are irradiated. Furthermore, as one ages, risk of cancer induction from radiation exposure decreases more rapidly for the breast than for other radiosensitive organs. Organs at highest risk for cancer are the bladder with PEM and the colon with BSGI; these cancers, along with lung cancer, are also less curable than breast cancer. Thus, the distribution of radiation throughout the body adds to the risks associated with BSGI and PEM. Hendrick concluded that "results reported herein indicate that BSGI and PEM are not good candidate procedures for breast cancer screening because of the associated higher risks for cancer induction per study compared with the risks associated with existing modalities such as mammography, breast US [ultrasound], and breast MR imaging. The benefit-to-risk ratio for BSCI and PEM may be different in women known to have breast cancer, in whom additional information about the extent of disease may better guide treatment."

O'Connor et al estimated the lifetime attributable risk of cancer and cancer mortality from use of digital mammography, screen film mammography, PEM, and MBI. Only results for digital mammography and PEM are reported here. The study concluded that in a group of 100,000 women at age 80 years, a single digital mammogram at age 40 years would induce 4.7 cancers with 1.0 cancer deaths; 2.2 cancers with 0.5 cancer deaths for a mammogram at age 50; 0.9 cancers with 0.2 cancer deaths for a mammogram at age 60; and 0.2 cancers with 0.0 cancer deaths for a mammogram at age 70. Comparable numbers for PEM would be 36 cancers and 17

cancer deaths for PEM at age 40; 30 cancers and 15 cancer deaths for PEM at age 50; 22 cancers and 12 cancer deaths for PEM at age 60; and 9.5 cancers and 5.2 cancer deaths for PEM at age 70. The authors also analyzed the cumulative effect of annual screening between ages 40 and 80, as well as between ages 50 and 80. For women at age 80 who were screened annually from ages 40 to 80, digital mammography would induce 56 cancers with 15 cancer deaths; for PEM, the analogous numbers were 800 cancers and 408 cancer deaths. For women at age 80 who were screened annually from ages 50 to 80, digital mammography would induce 21 cancers with six cancer deaths; for PEM, the analogous numbers were 442 cancers and 248 cancer deaths. However, background radiation from age 0 to 80 is estimated to induce 2174 cancers and 1011 cancer deaths. These calculations, like all estimated health effects of radiation exposure, are based on several assumptions. Comparing digital mammography and PEM, two conclusions are clear: Many more cancers are induced by PEM than by digital mammography; and for both modalities, adding annual screening from 40 to 49 roughly doubles the number of induced cancers. In a benefit/risk calculation performed for digital mammography but not for PEM, O'Connor et al nevertheless reported that the benefit/risk ratio of annual screening is still approximately 3 to 1 for women in their 40s, although it is much higher for women 50 and older. Like Hendrick, the authors concluded that "if molecular imaging techniques [including PEM] are to be of value in screening for breast cancer, then the administered doses need to be substantially reduced to better match the effective doses of mammography."

As noted in the section on Practice Guidelines and Position Statements, the American College of Radiology assigns a relative radiation level (effective dose) of 10 to 30mSv to PEM. They also state that because of radiation dose, PEM and breast-specific gamma imaging in their present form are not indicated for screening.

Because the use of BSGI or molecular breast imaging (MBI) has been proposed for women at high risk of breast cancer, it should be mentioned that there is controversy and speculation over whether some women, such as those with *BRCA* mutations, have heightened radiosensitivity. Of course, if women with *BRCA* mutations are more radiosensitive than the general population, the above estimates may underestimate the risks they face from breast imaging with ionizing radiation (ie, mammography, BSGI, MBI, PEM, [single-photon emission computed tomography] SPECT/CT, breast-specific CT, and tomosynthesis; ultrasound and MRI do not involve the use of radiation). More research will be needed to resolve this issue. Also, risks associated with radiation exposure will be greater for women at high risk of breast cancer, whether or not they are more radiosensitive, because they start screening at a younger age when risks associated with radiation exposure are increased.

Summary

Three principal studies on positron emission mammography (PEM) were reviewed. The first single-arm study provided preliminary data on sensitivity. Given that there is at least 1 imaging test for each potential use in breast cancer, any new or newly disseminating technology must be compared with existing modalities. Two nonrandomized studies (four articles) that compare the use of PEM and magnetic resonance imaging (MRI) or positron emission tomography (PET) imaging in presurgical planning are therefore important. However, each has its limitations, e.g., single site, lack of full blinding to results of alternate test, lack of adjustment for multiple comparisons, choice of comparator. It is also possible that apparent differences between PEM

and MRI, e.g., possibly higher sensitivity for MRI and potentially higher specificity for PEM, are due in part to selection of different operating points on the receiver operating characteristic (ROC) curve. Furthermore, ignoring the timing of testing in the 2012 Berg et al study may have biased results against MRI.

A 2011 study by Berg et al on the use of PEM in women with newly diagnosed breast cancer reported that PEM provided additional information (improved sensitivity) for detecting ductal carcinoma in situ (DCIS), but this finding requires replication in additional studies. This study also included several subgroup comparisons (e.g., women with no sign of multicentric or multifocal disease); a better study design would compare PEM with MRI in women before biopsy and follow them through to treatment, and ideally afterward, to gauge patient outcomes. A companion article reported that MRI was far more sensitive than PEM for detecting contralateral cancer, although MRI was somewhat less specific.

However, there was no statistical difference in positive predictive value (PPV) among women undergoing biopsy of the contralateral lesion. A substudy compared PEM with whole body positron emission tomography (PET) and with PET/computed tomography (CT) in separate small cohorts. Although PEM was found to be more sensitive than both imaging modalities, specificity, PPV, and negative predictive value were not statistically different. Further, clinical relevance of the findings is uncertain because PET imaging is not currently used in the diagnostic workup of newly diagnosed breast lesions. Finally, even if the addition of PEM to MRI improved accuracy, this finding must be weighed against potential risks from radiation exposure associated with PEM and lack of a full chain of evidence for some of these findings, specifically, that improved accuracy for some uses results in better patient outcomes. Thus, because impacts on net health outcome are uncertain, PEM is considered investigational.

Practice Guidelines and Position Statements

American College of Radiology

The American College of Radiology includes PEM in two sets of Appropriateness Criteria: one on breast screening and the other on the initial diagnostic work-up of breast microcalcifications. In the first, PEM is given a rating of 2 (1, 2, 3=usually not appropriate) for its use in screening women at high or intermediate risk of breast cancer and a 1 for screening women at average risk of breast cancer. It also assigns a relative radiation level of 10 to 30 mSv. It also notes that "Radiation dose from BSGI and PEM are 15-30 times higher than the dose of a digital mammogram, and they are not indicated for screening in their present form." In the second set of appropriateness criteria, PEM was assigned a rating of 1 (usually not appropriate) for the initial work-up of all 18 variants of microcalcifications. The authors note "The use of magnetic resonance imaging (MRI), breast specific gamma imaging (BSGI), positron emission mammography (PEM), and ductal lavage in evaluating clustered microcalcifications has not been established…. In general, they should not be used to avoid biopsy of mammographically suspicious calcifications."

National Comprehensive Cancer Network

Current (version 2.2013) NCCN guidelines for breast cancer screening and diagnosis do not include PEM.

American Society of Clinical Oncology
Current (2013) ASCO guidelines for follow-up and management of breast cancer after primary treatment do not include PEM.

Key Words:
Positron emission tomography (PEM), the PEM 2400 PET Scanner

Approved by Governing Bodies:
In August 2003, the PEM 2400 PET Scanner (PEM Technologies, Inc.) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices for use in "medical purposes to image and measure the distribution of injected positron emitting radiopharmaceuticals in human beings for the purpose of determining various metabolic and physiologic functions within the human body." In March 2009, FDA cleared the Naviscan PEM Flex™ Solo II High Resolution PET Scanner (Naviscan, Inc.; San Diego, California) for marketing through the 510(k) process for the same indication. The PEM 2400 PET Scanner was the predicate device. The newer device is described by the manufacturer as "a high spatial resolution, small field-of-view PET imaging system specifically developed for close-range, spot, ie, limited field, imaging."

On September 11, 2008, there was a class 2 recall of the Naviscan PET Systems Inc. PEM Flex™ Solo II PET Scanner due to "a report from a user indicating that the motorized compression exceeded 25 pounds of compression force during the pre-scan positioning of the patient." Software for the PEM Flex™ Solo I and PEM Flex™ Solo II PET scanners was recalled in August 2007. One report indicated that the Mexican medical company, Compañía Mexicana de Radiología SA de CV (CMR), acquired Naviscan in December 2013 and plans to file a new marketing approval application with FDA to sell the PEM Flex™ Solo II PET Scanner in the U.S. However, no applications from CMR were found on FDA websites.

Benefit Application:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Coding:
CPT Codes: There are no specific CPT codes for PEM.

The most appropriate codes would be:

78999: unlisted diagnostic nuclear medicine code,

Or the PET imaging limited area code might be used:

78811: Positron emission tomography (PET) imaging; limited area (eg, chest, head/neck).

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Policy History:

Medical Policy Panel, January 2011
Medical Policy Group, January 2011 **(2)**
Medical Policy Administration Committee, February 2011
Available for comment February 9 – March 25, 2011
Medical Policy Panel, June 2012

Medical Policy Group, July 2012 **(2):** Updated Key Points and References
Medical Policy Panel, June 2013
Medical Policy Group, September **(2):** No change in policy statement. Key Points and References updated
Medical Policy Panel, June 2014
Medical Policy Group, June 2014 **(3):** 2014 Updates to Key Points, Governing Bodies & References; add as a clarification to the policy statement "for all indications" – no change in context

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