Radioactive seed localization is used to identify the location of nonpalpable breast lesions, which have become more common with increasing use of breast cancer screening in asymptomatic women. This technique is used to target breast-conserving surgery or excisional biopsies, or to identify the location of the original cancer after neoadjuvant chemotherapy. A radiologist places a titanium “seed” containing radioactive I-125 with an 18-gauge needle using ultrasound, mammography, or stereotactic guidance. The surgeon then locates the seed and the breast tissue that needs to be removed, using a gamma probe. Alternative methods to localize nonpalpable breast lesions include wire localization, the traditional approach, or radio-guided occult lesion localization.

Related Policies

- None

Policy

Radioactive seed localization of nonpalpable breast lesions is expected to result in outcomes that are equivalent to alternatives such as wire localization or radio-guided localization, but may be more costly than alternatives. In this situation, the more costly alternative may be considered not medically necessary, and the least costly alternative may be considered medically necessary (See Policy Guidelines, and Benefit Application sections)

Policy Guidelines

Based on currently available evidence, health outcomes for radioactive seed localization and for alternative treatments appear to be equivalent. When outcomes are expected to be equivalent, the least costly alternative provision may be considered in determining medical necessity. When it is determined that a strategy using radioactive seed localization is more costly than one using alternatives (as determined by product pricing, provider charges, and/or other mechanisms), then radioactive seed localization may be considered not medically necessary using the Medical Policy Reference Manual definition of medical necessity.

There is no specific coding for radioactive seed localization of breast lesions. The CPT code for the placement of the seed is likely 19499 (unlisted procedure, breast) though it is possible that 19290 (preoperative placement of needle localization wire, breast) and 19291 (each additional lesion) might be reported. The seeds might be reported with A4641, A4648, or C1879.

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Medical Policy

6.01.57 Radioactive Seed Localization of Nonpalpable Breast Lesions

<table>
<thead>
<tr>
<th>Section</th>
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<td>6.0 Radiology</td>
<td>February 27, 2015</td>
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<th>Subsection</th>
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<td></td>
<td>February 27, 2015</td>
<td>February 2016</td>
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The code for the imaging used to localize the lesion would depend on the type of imaging used. Potential codes might be 76942 (ultrasonic guidance for needle placement (e.g., biopsy, aspiration, injection, localization device), imaging supervision and interpretation) or 77032 (mammographic guidance for needle placement, breast (e.g., for wire localization or for injection), each lesion, radiological supervision and interpretation).

Effective in 2014, there are CPT codes for insertion of breast localization device(s) that include radioactive seeds. Image-guided biopsies with placement of breast localization device(s) would be reported with codes 19081-19086, depending on the type of imaging guidance used and whether the lesion is an initial or subsequent lesion. Placement of breast localization device(s) without biopsy would be reported with codes 19281-19288, depending on the type of imaging guidance used and whether the lesion is an initial or subsequent lesion.

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Rationale**

**Background**

More nonpalpable lesions are currently detected (about 25% to 35% of breast cancers at diagnosis) due to the increased use of breast screening in asymptomatic women. These nonpalpable lesions require a localization technique to perform excisional biopsies or breast-conserving surgery (i.e., lumpectomy).

Radioactive seed localization on nonpalpable breast lesions uses radio-opaque titanium seed(s) containing radioactive I-125. These seeds are inserted by a radiologist using ultrasound or stereotactic guidance to identify the location of a nonpalpable breast lesion. They may be placed several days or weeks before surgery. The surgeon then uses a gamma probe to locate the radioactive seed and remove it with surrounding tissue. One study mentioned that the radiation dose associated with the I-125 seeds (0.29 mCi) was less than for a mammogram or chest X-ray. The radioactive dose in one group of studies ranged from 3.7 to 10.7 MBq (one megabecquerel [MBq] equals 0.027 millicuries). The seed was 4.5 x .8 mm, which has been described as similar to a grain of rice. The half-life of I-125 is 60 days and I-125 is a 27-keV source of gamma radiation. It can be detected on a different signal than the 140-keV Tc-99 that may be used for sentinel lymph node biopsy. Once the radioactive seed is removed, its presence in the tumor specimen is confirmed using the gamma probe, and the lack of radioactivity in the tumor cavity is also assessed to ensure that the radioactive seed has not been left in the breast. A disadvantage of radioactive seed localization is that special procedures must
be followed to safely handle and track the radioactive seed, before placement and after excision. In one public hospital (i.e., in clinical practice), a seed was lost following excision, and procedures were changed to prevent recurrence.

Radioactive seed localization may also be used to guide excision after neoadjuvant chemotherapy, which is performed primarily in women with locally advanced cancer in an effort to shrink the tumor. About 25% to 32% of these women are then able to have breast-conserving surgery rather than mastectomy. The challenge is that if there is a complete clinical and radiological response, it may be difficult to localize the original tumor bed. Pathologic confirmation of response is needed since there is residual microscopic cancer in about half of these patients. Radioactive seed localization can mark the tumor location before beginning neoadjuvant chemotherapy.

The traditional localization method for nonpalpable breast lesions is image-guided wire localization. This approach has limitations including the following: the wire can bend or be displaced (since the wire protrudes from the breast); there may be scheduling issues, because the wire should be placed on the same day as the surgery; and the radiologist may follow a different route to place the wire than the surgeon does to excise the lesion, which may make it more difficult to locate all of the lesion and may worsen cosmetic outcomes. The percentage of cases with positive margins following wire localization ranges from 14% to 47%.

An alternative developed in the late 1990s is radioguided occult lesion localization (ROLL). First, a twist marker is placed in the breast to mark the tumor. Prior to surgery, a liquid radioactive radiotracer (Tc-99) is injected next to the twist marker using image guidance. Again, the surgeon uses a gamma probe to locate the radiotracer and guide the incision. The main disadvantage of this approach is that the radiotracer has a short half-life of about 6 hours. It also does not provide a point source of radiation as radioactive seed localization does. An advantage is that Tc-99 may also be used for sentinel lymph node biopsy, so the same radiotracer is used for both purposes. On the other hand, the radioactive seed and Tc-99 for sentinel lymph node biopsy can also be used concurrently.

A final alternative is intraoperative ultrasound-guided resection, although it is discussed less frequently in this literature. It can only be used when the lesion can be detected using ultrasound. No studies comparing this approach to radioactive seed localization was found.

Radioguided seed localization was first tested in a randomized trial in 2001. Based on the number of publications and systematic reviews, there appears to have been an increased interest in this technique since about 2010.

Regulatory Status

The BrachySciences Radioactive Seed Localization Needle with AnchorSeed™ (Biocompatibles, Inc., Oxford, CT) received 510(k) marketing approval on October 18, 2011 (K111979). This device is indicated for the localization of suspicious tissues (non-palpable lesions) for excision with the use of radioactive seeds.

On December 19, 2012, the Best® Localization Needle with I-125 Seed received 510(k) marketing clearance (K122704). This device is indicated for breast localization under the direct supervision of a qualified physician. It consists of an iodine-125 seed and an 18-gauge 5-cm to 20-cm needle.

These devices are not always used for radioactive seed localization. Radioactive seeds approved for another indication (i.e., off-label) may also be implanted with an 18-gauge needle. These seeds were initially approved for permanent implantation (i.e.,
brachytherapy) in selected localized tumors such as prostate cancer. These seeds use $^{125}$I beads (activity from 0.1 to 1.0 mCi) encapsulated in a titanium tube. An example is International Isotopes Inc. [3RAD $^{125}$I Seed which received 510(k) marketing clearance September 21, 1999 (K992963).

**Literature Review**

Two randomized controlled trials (RCTs) compared radioactive seed localization to wire localization among patients scheduled for breast-conserving surgery or excisional biopsy. (1, 4) Gray and colleagues randomized 97 women in the U.S. with nonpalpable breast lesions to radioactive seed localization or wire localization; 51 had radioactive seed localization and 47, wire localization. (1) The method of randomization was not reported. Fifty-six patients underwent excisional biopsies for suspicious lesions that were judged inappropriate for percutaneous biopsy techniques, while 41 patients with a confirmed diagnosis of breast cancer by core needle biopsy had breast-conserving surgery (47% of radioactive seed localization patients and 37% of wire localization patients). On imaging, 42 patients had calcification and 55, a density. Both wire localization and radioactive seed localization were performed using ultrasound or mammography guidance. Surgery was performed up to 5 days later. Radiologists and patients rated the difficulty of the procedure following localization on a Likert scale from 1 (easiest) to 10 (most difficult), while the surgeons completed the same task after excision. Margins were considered to be positive if imprint cytology of the margins demonstrated malignant cells or if final histology demonstrated malignant cells <1 mm from any margin; only malignant tumors were included.

Fifty-two patients had invasive carcinoma; 9 had ductal carcinoma in situ; and 36 had benign lesions. There was no statistically significant difference in the number of patients with radioactive seed localization versus wire localization within each category. The outcomes for both localization techniques were the same for migration of the localization device (i.e., seed or wire); ability to locate the lesion during surgery; time for radiographic localization and for surgical excision; subjective ease of procedure for radiologists, patients, or surgeons; and volume of tissue removed. Specimen radiographs were used with wire localization but not with radioactive seed localization. There were fewer positive margins with radioactive seed localization than with wire localization (26% vs. 57%, p=0.02).

The second RCT published in 2011 was conducted at three Canadian sites and had a sample size of 205. (4) The participants had nonpalpable early stage breast cancer and were undergoing breast-conserving surgery. Randomization to radioactive seed localization or wire localization was centralized, concealed, and stratified (by surgeon for 7 surgeons). The two groups were similar except that multifocal disease was more common in the radioactive seed localization patients. The mean age was 60.9 years for the radioactive seed localization arm and 59.9 years for the wire localization arm. Exclusion criteria included male patients, pregnancy or lactation, multicentric or locally advanced disease, lobular carcinoma in situ (LCIS) only, and contraindications for breast-conserving surgery. Localization was performed using mammography or ultrasound on the day of surgery. The location was confirmed using 2-view mammography. An intention-to-treat analysis was performed. The power calculation was reported: A sample size of 333 patients could detect a 15% difference in positive margins across arms with 80% power and a 5% significance level.

In the radioactive seed localization arm, 18 had wire localization: 6 because the seed was not available at surgery; 3 because the seed would not deploy; and 2 because the seed was displaced. For 7 patients, no explanation was provided. In 3 cases, wire was
added to seed localization to bracket larger lesions. One seed migrated, and 2 wires did. One wire fell out during surgery.

All index lesions were removed. There were no differences between the two groups except the following: the mean operative time was shorter for radioactive seed localization (19.4 min for radioactive seed localization vs. 22.2 min for wire localization; p<0.001). Surgeons found excision following radioactive seed localization easier (p=0.008), while patients found it less painful (p=0.038). However, there was no statistically significant difference in patients’ anxiety level. There were no differences between groups in proportion of positive margins (10.5% for radioactive seed localization vs. 11.8% for wire localization) or reoperation rates. The results for positive margins were similar when the analysis was rerun based on the treatment patients received. Also, the percentage of positive margins was higher for ductal carcinoma in situ (DCIS) than for invasive cancer (20.4% vs. 9.2%; p=0.020). A related study analyzed factors associated with positive margins, including localization under stereotactic guidance, in situ disease, large tumor size, and multifocal disease. (5)

A retrospective analysis from the Netherlands compared radio-guided occult lesion localization (ROLL) using technetium-99(Tc-99) with radioactive seed localization using ultrasound guidance for seed placement. (6) Mammography was used to confirm correct placement of the twist marker or seed. Patients then had neoadjuvant chemotherapy and breast-conserving surgery (BSC) with wide local incision. Before surgery, patients underwent contrast-enhanced magnetic resonance imaging (MRI); those without enhancement in the original tumor area were considered complete radiological responders and had more limited excision to confirm complete pathologic response. (Carcinoma in situ was not counted). With ROLL, after injection of the radiotracer, scintigraphy with a dual-head gamma camera was performed to verify correct placement of the tracer. Radiologists and surgeons reported the time for each procedure and the level of difficulty on a Likert scale from 1(no difficulty) to 5(very difficult); patients reported pain and anxiety on a Likert scale from 0 (no pain) to 6 (severe pain).

After neoadjuvant chemotherapy, 24 patients had palpable lesions or a different localization method was performed. ROLL (n=83) or radioactive seed localization (n=71) was performed in 154 patients. No complications occurred during the localization procedure. For the patients undergoing the ROLL technique, 51% had complete radiological response and 30% had complete pathologic response. For patients with radioactive seed localization, 51% had complete radiologic response, and 38% had complete pathologic response. Weight of the excised specimen was similar between groups. Thirteen patients in each group had positive pathologic margins. Six patients in each group underwent further surgery, either additional local excision (1 ROLL patient and 3 radioactive seed localization patients) or mastectomy (5 ROLL patients and 3 radioactive seed localization patients). Other patients who had positive margins underwent adjuvant radiotherapy with a boost to the original tumor bed. There were no major peroperative complications in either group, with a median follow-up of 51 months (range, 5-67). After a mean follow-up of 22 months (range, 4-45 months), 6 (7%) of 83 ROLL patients had disease recurrence (including 1 DCIS local recurrence) and died due to metastatic disease. Eight (11%) of 71 patients undergoing radioactive seed localization developed metastatic disease and died within 24 months of follow-up; no isolated local recurrences occurred.

The 3 studies described are summarized in Table 1.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Gray 2001 (1)</th>
<th>Lovrics 2011 (2)</th>
<th>Donker 2013 (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison</td>
<td>RSL vs. WL</td>
<td>RSL vs. WL</td>
<td>RSL vs. ROLL</td>
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### Medical Policy

<table>
<thead>
<tr>
<th>Patient population</th>
<th>(randomized)</th>
<th>(RCT)</th>
<th>(nonrandomized)</th>
</tr>
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<tbody>
<tr>
<td>Undergoing excisional biopsy or BCS</td>
<td>Undergoing BCS</td>
<td>Undergoing BCS after neoadjuvant chemotherapy with complete or partial response</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>97*</td>
<td>205**</td>
<td>154</td>
</tr>
<tr>
<td>Mean/median age (yrs)</td>
<td>NR</td>
<td>RSL: 60.9; WL: 59.9</td>
<td>RSL: 49; ROLL: 50</td>
</tr>
<tr>
<td>Migration of localization device</td>
<td>No substantial migration for RSL or WL</td>
<td>RSL: 1 seed; WL: 2 wires and 1 wire fell out</td>
<td>NR</td>
</tr>
<tr>
<td>Removal of suspicious lesion</td>
<td>100% for both</td>
<td>100% for both</td>
<td>100% for both</td>
</tr>
<tr>
<td>Volume of extracted tissue</td>
<td>NS (RSL, 55.7 ml; WL, 73.5 ml)</td>
<td>NS (RSL, 191.1 cc; WL, 183.8 cc)</td>
<td>NS (RSL, 48 g; ROLL, 53 g)</td>
</tr>
<tr>
<td>Time for localization (min)</td>
<td>NS</td>
<td>NS</td>
<td>NR</td>
</tr>
<tr>
<td>Time for surgery (min)</td>
<td>NS</td>
<td>RSL, 19.4; WL, 22.2; p&lt;0.001</td>
<td>NR</td>
</tr>
<tr>
<td>Retrieval of titanium seed (RSL)</td>
<td>100% (without specimen radiograph)</td>
<td>NR but mean time = 2.3 min (SD=3.8 min); (with specimen radiograph)</td>
<td>100% (with specimen radiograph)</td>
</tr>
<tr>
<td>Positive margins</td>
<td>RSL, 26%; WL, 57%; p=0.02</td>
<td>ITT: NS (RSL, 10.5%; WL, 11.8%);*** As received treatment: NS (RSL, 10.4%; WL, 11.7%)</td>
<td>NS (RSL, 13%; ROLL, 13%)</td>
</tr>
<tr>
<td>Re-excision</td>
<td>NR</td>
<td>NS (RSL, 11.2%; WL, 13.1%)</td>
<td>RSL, 4%; ROLL, 1%</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>NR</td>
<td>NS</td>
<td>No major postoperative complications</td>
</tr>
<tr>
<td>Mastectomy numbers</td>
<td>NR</td>
<td>NS (RSL, 3.9%; WL, 2.9%)</td>
<td>RSL, 4%; ROLL, 6%</td>
</tr>
<tr>
<td>Radiologist rating of difficulty</td>
<td>NS</td>
<td>NS</td>
<td>NR</td>
</tr>
<tr>
<td>Surgeon rating of difficulty</td>
<td>NS</td>
<td>RSL easier than WL (p=0.008)</td>
<td>NR</td>
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<tr>
<td>Patient rating</td>
<td>NS</td>
<td>Pain with RSL less than with WL (p=0.038); Anxiety: NS</td>
<td>NR</td>
</tr>
</tbody>
</table>

KEY: BCS = breast-conserving surgery; NS = nonsignificant difference; p NR = p value not reported; ROLL = radioguided occult lesion localization; RSL = radioactive seed localization; SD = standard deviation; WL = wire localization

*Not including 4 women excluded after randomization because lesion no longer visible and 5, because of missing data.*
**Not including the following excluded after randomization: 15 from RSL arm and 13 from WL arm because not eligible, patient withdrew, management changed (to mastectomy or no surgery), surgery performed in hospital without approval from REB (not defined but presumably Research Ethics Board in Canada).

***Eighteen patients in the RSL arm received wire localization because the seed was not available (n=6) or the seed could not be placed (80% of these 12 occurred among radiologists with limited experience early in the trial). In another 3 patients, a wire was placed with the seed to bracket larger lesions.

Additional comparative articles include one by Hughes et al (2008), who compared radioactive seed localization in 383 patients with wire localization performed previously in 99 patients with nonpalpable lesions undergoing breast procedures (2,7). Patients were from 3 sites of the same institution. Seed migration more than 2 cm occurred in 1 patient, possibly due to a hematoma that developed after localization, and re-excision was performed during the initial surgery. Positive margins occurred in 27% of radioactive seed localization patients and in 46% of wire localization patients (p<0.001). Re-excision was undertaken in 8% of radioactive seed localization patients and in 25% of wire localization patients to achieve negative margins (p<0.001). Patients were asked to score the pain of the localization procedure and convenience of localization and surgery on a 10-point visual analog scale. Median pain scores were similar between groups (2.2 and 2.3; =0.9). There were no major adverse effects, but 6 radioactive seed localization patients (2%) and 1 wire localization patient (1%) had wound infections.

Groups from 2 cancer centers in the U.S. reported on their experience with radioactive seed localization. Diego et al (2014) compared outcomes for 128 women who underwent radioactive seed localization and 196 women who underwent wire localization before excisional breast biopsy for nonpalpable high-risk lesions during 2 consecutive years at the University of Pittsburgh Medical Center.8 Outcomes for excisional biopsies performed after radioactive seed localization during 1 year (postlearning curve) were collected prospectively and compared with retrospective outcomes for excisional biopsies performed after wire localization by the same surgeons (n=4) during the previous year. In both groups, mean patient age was 54 years, and the most common high-risk lesions were atypical hyperplasia (58%) and papilloma (23%). Forty-one percent of radioactive seeds and all wires (100%) were implanted/placed the day of surgery; 44% 2% and 13% of radioactive seeds were implanted 1, 2, and 3 days before surgery, respectively. Mean specimen volume was less in the radioactive seed localization group compared with the wire localization group (mean [SD], 26 [22] cm vs 37 [33] cm; ANOVA, p=0.001). There was no statistical between-group difference in mean operating room time (27 minutes in both groups; analysis of variance [ANOVA], p=0.9), despite greater trainee presence in the radioactive seed localization group; proportion of patients with additional tissue removed after specimen radiograph (3% in both groups; chi-square, p=0.4); proportion of target lesions retrieved (99% in the radioactive seed localization group vs 98% in the wire localization group; chi-square, p=0.5); or the proportion of patients upstaged to carcinoma (5% in the radioactive seed localization group vs 6% in the wire localization group; chi-square, p=0.5). All implanted radioactive seeds were retrieved at surgery.

In a similar study, researchers from Memorial Sloan-Kettering Cancer Center compared outcomes for 431 women who underwent radioactive seed localization and 256 women who underwent wire localization before lumpectomy for invasive or intraductal cancers during 2 consecutive 6-month periods.9 Outcomes for the radioactive seed localization group were collected prospectively during the first 6 months of use, and for the wire localization group, retrospectively during the previous 6 months. Surgeons (n=10) and
radiologists did not change between study time periods. Median patient age was approximately 60 years in both groups (Wilcoxon test, p=0.31), and 77% of patients in both groups had invasive cancer. The proportion of patients with features known to impact the probability of positive margins, such as tumor size, presence of an extensive intraductal component, or pure DCIS, was similar between groups. Ninety percent of radioactive seeds were implanted the day before surgery, and all wires (100%) were placed the morning of surgery. There was no statistical between-group difference in the incidence of positive margins (tumor on ink) or close margins (≤1 mm from ink) (total 25% in both groups; chi-square, p=0.38); reoperations to improve margins (approximately 23% in both groups; chi-square, p=0.83); specimen volume (median [range], 21 cm³ [0.2-311] in the radioactive seed localization group vs 19 cm³ [0.9-198] in the wire localization group; Wilcoxon test, p=0.074); or operative time for lumpectomy alone (Wilcoxon test, p=0.18) or lumpectomy with axillary lymph node dissection (Wilcoxon test, p=0.86). Operative time for lumpectomy plus sentinel lymph node biopsy was longer in the radioactive seed localization group compared with the wire localization group (median [range], 55 minutes [29-140] vs 48 minutes [12-110]; Wilcoxon test, p<0.001), which was attributed to use of a more complex probe capable of detecting both I-125 and T-99.

Rao et al (2010) reported on their experience using radioactive seed localization in a public hospital, in a retrospective matched-pair analysis of patients undergoing wire localization during the same period (10). One seed was lost after excision (i.e., it was not in the excised specimen) and was assumed discarded in the surgical drapes or suctioned fluid. Procedures were modified after this event to prevent recurrence. The study reported on 50 successful seed localizations in cancer patients and the matched controls. All seeds were recovered, and there was no seed migration. Re-excision rate was 42% for radioactive seed localization and 54% for wire localization. This difference was not statistically significant (p=0.46), which the authors attributed to small sample size.

In addition to these comparative studies, several single-arm studies report on radioactive seed localization (11-15). Gobardhan et al (2013) examined the use of radioactive seed localization in 85 patients undergoing neoadjuvant chemotherapy and BCS for invasive cancer (11). Another 4 patients independently requested mastectomy, and 8 were scheduled for mastectomy based on tumor characteristics; they were not included in the analysis. Thirty-two of 85 patients had multifocal tumors; 23 patients had more than 1 seed placed. Seeds were in place for a median of 4 months (range, 0-8). All patients received radiotherapy after BCS, and some received hormonal therapy or trastuzumab, as appropriate. After chemotherapy, 26 patients achieved clinically CR, and 51 achieved PR. No residual tumor, i.e., pathologically CR, occurred in 19 patients (36%), and resection was microscopically complete in 78 patients (92%). Four patients had focally involved margins and had a higher radiation boost to the tumor bed; 3 patients had extensively involved margins and had mastectomies. No re-excisions were performed, nor were there any wound healing problems. At a mean follow-up of 11 months, there were no local recurrences.

McGhann et al (2011) reported on a retrospective review of 1000 consecutive radioactive seed localizations in 978 patients after percutaneous biopsy at a single U.S. institution (12). Some of these cases were reported by Hughes and colleagues (2) in 2008. Breast surgery was performed by 3 surgeons. Based on final pathology, 55% of lesions were invasive cancer; 22%, DCIS; 11% atypical hyperplasia; and 13% benign pathologic lesions. In 46% of cases, intraoperative re-excision was performed based on surgeon or pathologist opinion. Fifteen percent of cancer cases underwent a second procedure for re-excision when the final margins were less than 2 mm. At mean follow-up of 33 months (range, 0.03-90.6), 9 patients experienced a local recurrence; there were no regional or distant recurrences. Of 1148 seeds deployed, there was seed displacement during
successful lesion excision for 30; vasovagal response on seed deployment for 4; failure to deploy seed properly on first attempt for 3; and for 1 each, wrong incision or seed migration preoperatively. All radioactive seeds were retrieved.

Van Riet et al (2010) reported on radioactive seed localization among 325 consecutive women with nonpalpable, biopsy-confirmed breast cancer.14 Women with DCIS on core biopsy were excluded. Seed localization failed in 3 women and was redone successfully on the second attempt. The seed was dislodged during surgery in 6 patients, 4 of whom underwent re-excision after specimen radiology. Complete resection was accomplished in 310 procedures, and 15 had positive margins.

A 2011 study of seed migration after radioactive seed localization found that in 45 patients with radioactive seeds in situ for a mean of 59.5 days (range, 3-136), mean (SD) seed migration was 0.9 mm (1.0).16 Cox et al (2003) assessed whether specimen radiographs are required during breast surgery or biopsy after radioactive seed localization.17 Radiographs are routinely used during surgery after wire localization to ensure that the suspected lesion has been excised. The aim of the study was to demonstrate that specimen radiographs are not needed with radioactive seed localization when the seed is within 1 cm of the lesion, the surgeon removed the seed without dislodging it from the tissue, and the pathologist can grossly identify the lesion and retrieve the seed. In an analysis of 124 women (142 lesions), specimen radiographs were performed on 32 lesions. This occurred more often with microcalcifications than with masses and in women undergoing excisional biopsy than in those having BCS.

Authors overlap in 6 of the studies previously discussed(1,2,7,12,17,18).

A meta-analysis of radioactive seed localization versus wire localization included both of the randomized studies previously discussed (although for unstated reasons, the authors categorized Gray et al (2001)1 as a cohort study with a control group) and 3 other cohort studies with control groups. The authors noted that the quality of the studies was limited, with only 1 RCT, and cohort studies with retrospective wire localization control groups.1,2,4,7,10 Two outcomes had moderate but statistically insignificant heterogeneity at the 0.05 level. Fixed effect models were used in all cases. The results are as follows: Positive margins for wide local incision were significantly less likely for radioactive seed localization versus wire localization (odds ratio [OR], 0.51; 95% confidence interval [CI], 0.36 to 0.72; p<0.001) for 5 trials. Reoperations were less likely for radioactive seed localization (OR, 0.47; 95% CI, 0.33 to 0.69; p<0.001) for the 4 trials included. Shorter surgery is significantly more likely using radioactive seed localization versus wire localization (mean difference, -1.32 min; 95% CI, -2.32 to -0.32; p=0.01) for the 2 trials included. Based on 2 trials, there was no statistically significant difference in the volume of breast tissue excised during surgery (mean difference, 1.46 cm3; 95% CI, -22.35 to 25.26; p=0.90). Results of this meta-analysis should be interpreted with caution given the quality of the included studies. Barentsz et al (2013) conducted a systematic review of 6 studies, all previously discussed(20).

Section Summary

The highest quality study on the use of radioactive seed localization versus another localization technique is the 2011 randomized controlled trial by Lovrics et al.4 The study was unblinded, given the obvious nature of the different techniques. Results showed no statistically significant differences between the 2 techniques, except for a slightly shorter time to perform radioactive seed localization, less difficult excisions reported by surgeons, and reduced pain (but not anxiety) reported by patients. A smaller randomized study by Gray et al 2001 reported significantly fewer positive margins, but other metrics in Table 1 did not differ statistically between modalities or were not reported.1 More favorable
results for radioactive seed localization (i.e., fewer positive margins or re-excisions) were reported inconsistently in other studies and may have been impacted by tumor characteristics. Therefore, the comparative performance of radioactive seed localization versus wire localization or radio-guided occult lesion localization can be assessed reliably only in randomized trials. The limited evidence does not demonstrate a difference in performance between radioactive seed localization and either wire localization or, with even more limited evidence, radio-guided occult lesion localization. Currently, online site ClinicalTrials.gov lists no ongoing studies of radioactive seed localization.

**Ongoing and Unpublished Clinical Trials**

Online site ClinicalTrials.gov currently lists 1 active, open-label trial of radioactive seed localization (NCT01901991). Patients at a single center in Denmark who have a nonpalpable breast lesion (carcinoma in situ or invasive carcinoma) will be randomized 1:1 to wire-guided localization (with ultrasound or mammography guidance) or radioactive seed localization (with ultrasound guidance). Lesion localization will be confirmed by mammography in both treatment arms. Outcomes include reoperation rates, amount of excised tissue, and breast surgery duration. Estimated enrollment is 410 patients, and expected completion date is April 2017.

**Summary of Evidence**

Radioactive seed localization is an alternative technique to wire localization or radio-guided occult lesion localization in women with nonpalpable breast lesions. It may be used before excisional biopsy or breast-conserving surgery, with or without neoadjuvant chemotherapy. Clinical outcomes of these 3 localization techniques are likely to be equivalent. Therefore, radioactive seed localization of nonpalpable breast lesions may be considered **not medically necessary** when it is determined that it is generally more costly than wire localization or radio-guided occult lesion localization.

**SUPPLEMENTAL INFORMATION**

**Practice Guidelines and Position Statements**

A search of the National Guideline Clearinghouse (www.guidelines.gov) and National Comprehensive Cancer Network (www.nccn.org) websites yielded no policies on the use of radioactive seed localization in the breast.

**American College of Radiology**

In 2013, ACR issued a practice guideline for imaging management of DCIS and invasive breast carcinoma.21 Both wire localization (using mammographic, sonographic, or magnetic resonance imaging [MRI] guidance) and radioactive seed localization (using mammographic or sonographic guidance) as techniques for preoperative image-guided localization of nonpalpable breast lesions.

**U.S. Preventive Services Task Force Recommendations**

Use of radioactive seed localization is not a preventive service.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing Clinical Trials**

No ongoing studies on this technology were found at clinicaltrials.gov.
Summary
Radioactive seed localization is an alternative technique to wire localization or radioguided occult lesion localization among women with nonpalpable breast lesions. It may be used before excisional biopsy or breast-conserving surgery, with or without neoadjuvant chemotherapy. The clinical outcomes of these three localization techniques are likely to be equivalent. Therefore, radioactive seed localization of nonpalpable breast lesions may be considered not medically necessary when it is determined that it is generally more costly than wire localization or radioguided occult lesion localization.

Practice Guidelines and Position Statements
A search of online sites guidelines.gov, acr.org, and nccn.org yielded no policies on the use of radioactive seed localization in the breast.

Medicare National Coverage
There is no Medicare national coverage determination on radioactive seed localization for nonpalpable breast lesions.

References

**Documentation Required for Clinical Review**

Please provide the following documentation:

- History and physical including: previous treatment plan and response
- Consultation report including: previous treatment and response
  - Laboratory report(s)
  - Operative report(s)
Medical Policy

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

MN/NMN

The following services may be considered medically necessary when policy criteria are met. Services are considered not medically necessary when policy criteria are not met.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>19081</td>
<td>Biopsy, breast, with placement of breast localization device(s) (e.g., clip, metallic pellet), when performed, and imaging of the biopsy specimen, when performed, percutaneous; first lesion, including stereotactic guidance</td>
</tr>
<tr>
<td></td>
<td>19082</td>
<td>Biopsy, breast, with placement of breast localization device(s) (e.g., clip, metallic pellet), when performed, and imaging of the biopsy specimen, when performed, percutaneous; each additional lesion, including stereotactic guidance (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td></td>
<td>19803</td>
<td>Biopsy, breast, with placement of breast localization device(s) (e.g., clip, metallic pellet), when performed, and imaging of the biopsy specimen, when performed, percutaneous; first lesion, including ultrasound guidance</td>
</tr>
<tr>
<td></td>
<td>19804</td>
<td>Biopsy, breast, with placement of breast localization device(s) (e.g., clip, metallic pellet), when performed, and imaging of the biopsy specimen, when performed, percutaneous; each additional lesion, including ultrasound guidance (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td></td>
<td>19805</td>
<td>Biopsy, breast, with placement of breast localization device(s) (e.g., clip, metallic pellet), when performed, and imaging of the biopsy specimen, when performed, percutaneous; first lesion, including magnetic resonance guidance</td>
</tr>
<tr>
<td></td>
<td>19806</td>
<td>Biopsy, breast, with placement of breast localization device(s) (e.g., clip, metallic pellet), when performed, and imaging of the biopsy specimen, when performed, percutaneous; each additional lesion, including magnetic resonance guidance (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td></td>
<td>19281</td>
<td>Placement of breast localization device(s) (e.g., clip, metallic pellet, wire/needle, radioactive seeds)</td>
</tr>
<tr>
<td>Procedure Code</td>
<td>Description</td>
<td></td>
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<tr>
<td>----------------</td>
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<td></td>
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<tr>
<td>19282</td>
<td>Placement of breast localization device(s) (e.g., clip, metallic pellet, wire/needle, radioactive seeds), percutaneous; first lesion, including mammographic guidance (List separately in addition to code for primary procedure)</td>
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<td>19283</td>
<td>Placement of breast localization device(s) (e.g., clip, metallic pellet, wire/needle, radioactive seeds), percutaneous; first lesion, including stereotactic guidance</td>
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<tr>
<td>19284</td>
<td>Placement of breast localization device(s) (e.g., clip, metallic pellet, wire/needle, radioactive seeds), percutaneous; each additional lesion, including stereotactic guidance (List separately in addition to code for primary procedure)</td>
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<tr>
<td>19285</td>
<td>Placement of breast localization device(s) (e.g., clip, metallic pellet, wire/needle, radioactive seeds), percutaneous; first lesion, including ultrasound guidance</td>
<td></td>
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<tr>
<td>19286</td>
<td>Placement of breast localization device(s) (e.g., clip, metallic pellet, wire/needle, radioactive seeds), percutaneous; each additional lesion, including ultrasound guidance (List separately in addition to code for primary procedure)</td>
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<tr>
<td>19287</td>
<td>Placement of breast localization device(s) (e.g., clip, metallic pellet, wire/needle, radioactive seeds), percutaneous; first lesion, including magnetic resonance guidance</td>
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<tr>
<td>19288</td>
<td>Placement of breast localization device(s) (e.g., clip, metallic pellet, wire/needle, radioactive seeds), percutaneous; each additional lesion, including magnetic resonance guidance (List separately in addition to code for primary procedure)</td>
<td></td>
</tr>
</tbody>
</table>

**ICD-9 Procedure**: None

**ICD-10 Procedure**: None

**ICD-9 Diagnosis**: All Diagnoses

**ICD-10 Diagnosis**: For dates of service on or after 10/01/2015; All Diagnoses
Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/27/2015</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine medical necessity.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.