Radioactive Seed Localization of Nonpalpable Breast Lesions

Description

Radioactive seed localization is used to detect nonpalpable breast lesions, which have become more common with increasing use of breast cancer screening in asymptomatic women. This technique is used before breast-conserving surgery or excisional biopsies, or to identify the location of an original cancer after neoadjuvant chemotherapy. A radiologist places a titanium "seed" containing radioactive iodine 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.

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 (BCS; ie, lumpectomy).

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 (because 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 complicate locating all of the lesion and worsen cosmetic outcomes. The percentage of cases with positive margins after wire localization is 14% to 47%.

Radioactive seed localization of nonpalpable breast lesions uses radio-opaque titanium seed(s) containing radioactive iodine 125 (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 I-125 seeds (0.29 mCi) was less than that for a mammogram or chest radiograph. The range of radioactive doses in 1 group of studies was 3.7 to 10.7 MBq (1 MBq=0.027 mCi). Seeds were 4.5x0.8 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 technetium 99 (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. Lack of radioactivity in the tumor cavity also is 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.

Radioactive seed localization also may 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. A proportion of these women (25%-32%) are then able to have BCS rather than mastectomy. The challenge is that if there is a complete clinical and radiologic response, it may be difficult to localize the original tumor bed. Pathologic confirmation of response is needed because there is residual microscopic cancer in about half of these patients. Radioactive seed localization can mark the tumor location before beginning neoadjuvant chemotherapy.

An alternative to wire localization or radioactive seed localization, developed in the late 1990s, is radio-guided occult lesion localization. First, a twist marker is placed in the breast to identify the tumor. Before surgery, a liquid radioactive radiotracer (Tc-99) is injected next to the twist marker using image guidance. 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 (≈6 hours). It also does not provide a point source of radiation. An advantage is that Tc-99 may be used for sentinel lymph node biopsy, so the same radiotracer is used for both purposes. Alternatively, a radioactive seed and Tc-99 for sentinel lymph node biopsy can be used concurrently. Another alternative is intraoperative ultrasound-guided resection, although the procedure is discussed less frequently in this literature. It can only be done when the lesion is detectable by ultrasound.

**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 (ie, off-label) may also be implanted with an 18-gauge needle. These seeds were initially approved for permanent implantation (ie, brachytherapy) in selected localized tumors such as prostate cancer. These seeds use I-125 beads (activity from 0.1 to 1.0 mCi) encapsulated in a titanium tube. An example is International Isotopes Inc. I3RAD I-125 Seed, which received 510(k) marketing clearance September 21, 1999 (K992963). FDA Product code: KXX

**Related Policies**

None
Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Radioactive seed localization of nonpalpable breast lesions may be considered medically necessary for the purposes of locating lesions to guide excisional biopsy or breast-conserving surgery, because the clinical outcomes are likely to be equivalent to wire localization.

Rationale

Systematic Reviews

Several systematic reviews of the literature have compared radioactive seed localization (RSL) to other localization methods. A 2015 Cochrane review evaluated randomized controlled trials (RCTs) comparing localization techniques to guide surgical excision of nonpalpable breast lesions. Fourteen RCTs were identified; 2 compared RSL with wire localization (WL), 6 compared radio-guided occult lesion localization (ROLL) with WL, and 3 used less common techniques. The primary outcomes were successful localization of the lesion, successful excision of the lesion, positive excision margins, and need for further excision. Meta-analyses were conducted for several of these outcomes for RSL and WL. There was no significant difference in the rate of successful excision with RSL or WL (relative risk [RR], 1.00; 95% CI [confidence interval], 0.99 to 1.01; rate of positive margins, RR=0.67; 95% CI, 0.43 to 1.06). The authors concluded that the published evidence does not clearly support 1 localization method over another.

A 2015 meta-analysis by Pouw et al included studies evaluating RSL, with or without a comparator intervention. Sixteen studies were identified; the number of patients in individual studies ranged from 13 to 2222. Among the included studies, 6 compared RSL with WL, 1 compared RSL with ROLL, and the remaining studies were uncontrolled. However, this systematic review only reported outcomes for the RSL cases. The primary outcomes were irradicality (ie, positive margins) and need for re-excision. In the 16 studies, the average proportion of patients with irradicality was 10.3% (range, 3%-30.3%) and the average re-excision rate was 14.2% (range, 4%-42%).

In 2013, Ahmet et al published a systematic review and meta-analysis of RCTs and controlled nonrandomized studies of RSL and WL. Positive margins for wide local incision were significantly less likely for RSL versus WL (odds ratio [OR], 0.51; 95% CI, 0.36 to 0.72; p<0.001) for 5 studies. Reoperations were less likely for RSL (OR=0.47; 95% CI, 0.33 to 0.69; p<0.001) for the 4 trials included. Shorter surgery was significantly more likely using RSL than WL (mean difference, -1.32 min; 95% CI, -2.32 to -0.32 min; 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 cm³; p=0.90).

Randomized Controlled Trials

Three RCTs (2 included in the Cochrane reviews, 1 newer RCT) are described below and summarized in Table 1.
Gray et al (2001) randomized 97 U.S. women with nonpalpable breast lesions to RSL (n=51) or WL (n=47). The method of randomization was not reported. Fifty-six patients underwent excisional biopsies for suspicious lesions judged inappropriate for percutaneous biopsy techniques, and 41 patients with a confirmed diagnosis of breast cancer by core needle biopsy had breast-conserving surgery (BCS; 47% of RSL patients, 37% of WL patients). On imaging, 42 patients had calcification, and 55 had a density. Both WL and RSL were performed using ultrasound or mammography guidance. Surgery was performed up to 5 days later. Radiologists and patients rated the difficulty of the procedure after localization on a Likert scale from 1 (easiest) to 10 (most difficult), and surgeons completed the same rating after excision. Margins were considered positive if imprint cytology of the margins demonstrated malignant cells or if final histology demonstrated malignant cells less than 1 mm from any margin; only malignant tumors were included.

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

In 2011, Lovrics et al published findings of an RCT with 205 patients. Participants had nonpalpable early-stage breast cancer and were undergoing BCS. Randomization to RSL or WL was centralized, concealed, and stratified (by surgeon for 7 surgeons). The 2 groups were similar except that multifocal disease was more common in the RSL patients. Mean age was about 60.9 years for both arms. Exclusion criteria included male patients, pregnancy or lactation, multicentric or locally advanced disease, lobular carcinoma in situ only, and contraindications for BCS. Localization was performed using mammography or ultrasound on the day of surgery. Tumor location was confirmed using 2-view mammography. An intention-to-treat analysis was performed, and the power calculation was reported: A sample size of 333 patients could detect a 15% difference in positive margins across arms with 80% power at a 5% significance level.

In the RSL arm, 18 patients had WL: 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 and 2 wires migrated and 1 wire fell out during surgery.

All index lesions were removed. There were no between-group differences, except the following: mean surgical time was shorter for RSL (19.4 min vs 22.2 min, respectively; p<0.001); surgeons found excision after RSL easier (p=0.008); and patients found RSL less painful (p=0.038). However, there was no statistically significant difference in patients’ anxiety level. There were no between-group differences in proportion of positive margins (10.5% for RSL vs 11.8% for WL) or reoperation rates. Results for positive margins were similar when the analysis was rerun based on the treatment patients received (per protocol analysis). Also, the percentage of positive margins was higher for DCIS (20.4%) than for invasive cancer (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.
In 2016, Bloomquist et al published an RCT comparing RSL (n=70) and WL (n=55). The trial included adult women with nonpalpable invasive carcinoma or DCIS who were eligible for BCS. Multifocal disease and extensive disease requiring bracketing were not exclusion criteria. The primary outcomes were patient-reported assessment of procedure-related pain and overall convenience of the procedure. Patients in the RSL group completed a questionnaire immediately after the procedure and patients in the WL group completed a questionnaire at the first postoperative visit. The difference in timing could bias outcomes (eg, patients may remember pain during the procedure differently by the time they had a postoperative visit). Pain was measured on a 1- to 5-point Likert-type scale (1=no pain and 5=severe pain). Convenience was also rated on a 1-to-5 scale (1=poor convenience and 5=excellent convenience). Median pain scores during the procedure did not differ significantly between groups. However, the convenience of RSL was rated significantly higher than WL. The median convenience score was 5 in the RSL group and 3 in the WL group (p<0.001).

Surgical outcomes were also reported. There was no significant difference in the rate of positive margins (RSL=19.4% vs WL=15.3%; p=0.053). There were also no significant differences in the volume of extracted tissue: the mean volume was 77.0 cm² in the RSL group and 67.4 cm² in the WL group (p=0.67). All targeted lesions were successfully excised and there were no lost seeds or transected wires.

Table 1. Summary of Randomized Controlled Trials Comparing RSL and WL

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<thead>
<tr>
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<tbody>
<tr>
<td>Patient population</td>
<td>Undergoing excisional biopsy or BCS</td>
<td>Undergoing BCS</td>
<td>Undergoing BCS</td>
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<tr>
<td>Sample size</td>
<td>97</td>
<td>205</td>
<td>125</td>
</tr>
<tr>
<td>Migration of localization device</td>
<td>No substantial migration for either</td>
<td>• RSL: 1 seed</td>
<td>• RSL: 6 displaced seeds</td>
</tr>
<tr>
<td>Removal of suspicious lesion</td>
<td>100% for both</td>
<td>• WL: 2 wires; 1 wire fell out</td>
<td>• WL: 7 displaced wires</td>
</tr>
<tr>
<td>Volume of extracted tissue</td>
<td>RSL=55.7 mL vs WL=73.5 mL (NS)</td>
<td>RSL=191.1 cc vs WL=83.8 cc (NS)</td>
<td>NS</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 vs WL=22.2; (p=0.001)</td>
<td>NR</td>
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<tr>
<td>Positive margins</td>
<td>RSL=26% vs WL=57% (p=0.02)</td>
<td>(RSL=10.5% vs WL=11.8% (NS)</td>
<td>RSL=19.4% vs WL=15.3% (NS)</td>
</tr>
<tr>
<td>Re-excision</td>
<td>NR</td>
<td>RSL=11.2% vs WL=13.1% (NS)</td>
<td>NR</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>RSL=3.9% vs WL=2.9% (NS)</td>
<td>NR</td>
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<td>Radiologist rating of difficulty</td>
<td>NS</td>
<td>NS</td>
<td>NR</td>
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<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)</td>
<td>Pain (NS)</td>
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BSC: breast-conserving surgery; NR: not reported; RCT: randomized controlled trial; RSL: radioactive seed localization; WL: wire localization.
Section Summary

Three RCTs and meta-analyses have generally not found statistically significant differences in outcomes with RSL and the generally accepted standard, WL. In all cases reported in RCTs, the suspicious lesions were successfully removed using either method. The rates of positive margins also did not differ significantly between RSL and WL. There are fewer data on other outcomes (eg, re-excision rates, complication rates), but the available studies do not suggest significant differences between RSL and WL. Additional adequately powered and well-conducted RCTs would further clarify any differences in outcomes between RSL and WL. Other RCTs included in a Cochrane review found similar outcomes with ROLL and WL; however, RCTs directly comparing RSL and ROLL would strengthen the evidence base.

Practice Guidelines and Position Statements

American College of Radiology

In 2013 (amended in 2014), the American College of Radiology issued a practice guideline for imaging management of ductal carcinoma in situ and invasive breast carcinoma. Both wire localization (using mammographic, sonographic, or magnetic resonance imaging guidance) and radioactive seed localization (using mammographic or sonographic guidance) as techniques for preoperative image-guided localization of nonpalpable breast lesions are discussed as techniques to provide guidance to the surgeon.

U.S. Preventive Services Task Force Recommendations

Not applicable

Summary of Evidence

For individuals who have a nonpalpable breast lesion who are undergoing a procedure that requires lesion localization who receive radioactive seed localization, the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are other test performance measures, resource utilization, and treatment-related morbidity. There are 3 RCTs comparing radioactive seed localization and wire localization, and overall they have found similar outcomes (eg, rate of successful excision, rate of positive margins) with both techniques. Systematic reviews have also found that outcomes with both localization methods are similar. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Medicare National Coverage

There is no national coverage determination (NCD).

References


### Policy History

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<th>Date</th>
<th>Action</th>
<th>Reason</th>
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<tr>
<td>December 2013</td>
<td>New Policy</td>
<td>Policy updated with literature review; references 3, 8-9 added; reference 21 updated. No change to policy statement.</td>
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<tr>
<td>March 2015</td>
<td>Update Policy</td>
<td>Policy updated with literature review; references 4-5, and 9 added. No change to the policy statement.</td>
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### Keywords

Radioactive localization, breast

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This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 17, 2017 and is effective April 15, 2017.

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