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Coverage Policy

Cryoablation of a benign or malignant breast lesion is considered experimental, investigational or unproven.

Overview

This Coverage Policy addresses the use of cryoablation, also referred to as cryosurgery or cryosurgical ablation for the treatment of benign or malignant breast lesions.

General Background

Cryoablation, also referred to as cryosurgery or cryosurgical ablation, has been proposed as a minimally invasive alternative for the treatment of fibroadenomas and cancers of the breast. Fibroadenomas are benign, solid tumors comprised of glandular breast tissue and stromal (connective) tissue, and are the most common breast tumor in women younger than age thirty. Although fibroadenomas may occur at any age, they are rarely seen as new masses in women after the age of 40–45. Fibroadenomas may stop growing, spontaneously regress, or may increase in size. Simple fibroadenomas do not increase breast cancer risk. Those that contain macrocysts, sclerosing adenosis, calcifications, or apocrine changes are referred to as complex fibroadenomas, and are associated with a slightly increased risk of breast cancer. Most physicians and patients choose conservative management for pathology-confirmed fibroadenomas, with periodic clinical examination and ultrasound or
mammography follow-up. Others opt for surgical removal, especially if the mass is growing and the shape of the breast is altered.

Excluding cancers of the skin, breast cancer is the most frequently diagnosed cancer in women. Diagnostic evaluation is usually triggered by symptoms, by the detection of a palpable breast mass by the physician or patient, or by detection of a suspicious mass on screening mammography. Breast cancer is confirmed by histopathological findings obtained during a breast biopsy. Treatment of breast cancer is based on tumor size, stage, and other characteristics, as well as patient preference. Treatment may include lumpectomy (i.e., surgical removal of the tumor with confirmation of clear margins) or mastectomy (i.e., surgical removal of the breast and selected axillary lymph nodes), and may also include radiation therapy, chemotherapy, hormone therapy, or targeted biologic therapy. Cryoablation has been proposed as a minimally invasive alternative to lumpectomy, and as an alternative to needle wire localization in patients undergoing lumpectomy for breast cancer.

Cryoablation achieves tissue necrosis by alternately freezing and thawing targeted tissue. A cryoprobe is inserted percutaneously into the center of the lesion using ultrasound guidance. A cooling medium is circulated through the probe, and the cells in proximity to the cryoprobe are brought to very low temperatures, resulting in the formation of intracellular ice that in turn shears the cell membranes. Cells located further from the cryoprobe freeze at a slower rate, with ice formation primarily in the extracellular space, creating a hypertonic environment. Water is driven out of the cells, and dehydration causes additional membrane damage. During the thaw, water returns from the extracellular space into the shrunken cells, resulting in intracellular edema and lysis. This destructive process is repeated in a second freeze cycle. The ablative process is completed after several days, as capillary endothelial damage caused by the ultracold temperatures results in leakage, thrombolysis, and target tissue anoxia (NCI, 2015; Kaufman, 2004b; Whitworth, 2005).

U.S. Food and Drug Administration (FDA)
Numerous cryosurgical devices have received FDA approval for various indications through the 510k process. Examples include Sanarus Visica™ Treatment System (Sanarus Medical, Inc., Pleasanton, CA) and the SeedNet/SeedNetGold System, CryoThera System, Cryo-Hit System, referred to collectively as the SeedNet Family (Galil Medical Ltd, Israel). The IceSense3 (IceCure Medical LTD., Israel) received 510k approval in 2010. The FDA stated it “is intended for cryogenic destruction of tissue during surgical procedures. The IceSense3 is indicated for use as a cryosurgical tool in the fields of general surgery, dermatology, thoracic surgery, gynecology, oncology, proctology, and urology. The IceSense3 may be used with an ultrasound device to provide real-time visualization of the cryosurgical procedure”. However, a 2017 American Society of Breast Surgeons (ASBS) Consensus Guideline states “At this time, there are no FDA approved ablative or minimally invasive treatments for breast cancer”.

Literature Review: Cryoablation of Breast Fibroadenomas
Small prospective and retrospective case series report the use of in-office liquid nitrogen cryoablation. However, they do not establish clear ‘successful’ long term health outcomes. Reported outcomes vary: engulfment of fibroadenoma in liquid nitrogen during the procedure, fibroadenoma is not palpable months or a year after cryoablation, fibroadenoma is soft months or a year after cryoablation compared to pre-ablation firmness, fibroadenoma is not found via ultrasound months or a year after cryoablation, and cosmetic appearance.

Lanza et al. (2015) conducted a systematic review evaluating percutaneous breast cancer cryoablation in 161 patients (five studies were prospective, two were retrospective). Of cryoablation procedures, 25 were performed under magnetic resonance (MR) imaging guidance, 129 were performed under ultrasound (US) guidance, and 32 were performed under computed tomography (CT) guidance. Complete local tumor control was noted in 73% of patients (mean follow-up, 8 months). No major complications were noted.

In a prospective case series, Golata et al. (2015) performed 60 office-based cryosurgical procedures in patients with histological confirmed benign fibroadenomas (maximum dimension of 3 cm). During the office-based, liquid nitrogen cryoablation procedure, continuous ultrasound monitoring was performed, verifying engulfment of the fibroadenoma. Patients attended four follow-up visits at 1 week, 3, 6 months and 1 year. At the 1-year follow-up, the fibroadenomas were gone in 93% of the cases. Cosmetic results at 12 months follow-up were reported as good or excellent in 100% by physician and in 97% by patients.
Nurko et al. (2005) evaluated six- and twelve-month data in the FibroAdenoma Cryoablation Treatment (FACT) registry. A total of 249 of 444 treated fibroadenomas were evaluated at least six months post-procedure, and 92 were evaluated at least 12 months post-procedure. Prior to cryoablation, 75% of fibroadenomas were palpable by the patient, and 100% were visualized on ultrasound. The treated site remained palpable in 46% of cases at six months, and in 32% of cases at 12 months. The remaining lesion was visible on ultrasound in 36% of cases at six months, and in 29% of cases at 12 months. Patient satisfaction was rated at 91% at six months and 88% at 12 months. The authors noted that patients should be made aware of the likely prolonged persistence of a palpable mass in the treated area. This is particularly important when the mass is not palpable prior to the procedure, since cryoablation-induced changes may result in the mass becoming palpable following the procedure.

Edwards et al. (2004) provided a retrospective summary from a national registry. A total of 53 sites treated fibroadenomas with cryoablation and reported procedural data on 310 lesions. Post-procedural follow-up at 6 and 12 months was available for 89 and 12 treated patients, respectively. The authors reported that at 6 and 12 months post-procedure, the remaining fibroadenoma volume progressively involuted.

Kaufman et al. published several case series evaluating cryoablation in the treatment of benign breast disease. It is unclear how many of the same patients are included in each analysis. The 2005 Kaufman case series reported outcomes of cryoablation treatment of fibroadenomas at a mean follow-up of 2.6 years (range 1.3–3.8 years). Of 70 fibroadenomas (57 patients), efficacy data was reported for 29 patients (32 fibroadenomas). Of 29 patients, five could still feel a residual mass, with three reporting progressive shrinkage of the treated area. Small fibroadenomas (≤ 2.0 cm) became non-palpable sooner than large fibroadenomas. Serial ultrasound confirmed resorption of the cryoablation debris. The median volume reduction of the residual debris was 89% at one year and 99% at a mean of 2.6 years. Gradual resorption was related to the original tumor size. Fifteen mammograms were available at follow-up. None had artifact from cryoablation that would adversely affect interpretation. Two had calcifications classified as benign and one had an asymmetric density attributed to probable nonspecific fibroglandular tissue.

Studies of cryoablation for the treatment of fibroadenomas consist primarily of nonrandomized retrospective and prospective case series with varying definitions of 'successful' outcomes. The majority of published studies include very small patient populations. Evidence from larger, well-designed clinical trials is needed to determine how this approach compares to alternatives such as no treatment other than periodic clinical examination and mammography or ultrasound follow-up.

**Literature Review: Cryoablation for Breast Cancer**

The American College of Surgeons Oncology Group Z1072 was a phase II trial exploring the effectiveness of cryoablation in the treatment of breast cancers (Simmons, et al., 2016). Eligible patients included those with unifocal invasive ductal breast cancer ≤2 cm, with <25 % intraductal component and tumor enhancement on MRI. A total of 19 centers contributed 99 patients, of which 86 patients (87 breast cancers) were evaluable for data analysis. The primary endpoint of Z1072 was the rate of complete tumor ablation, defined as no remaining invasive breast cancer (IBC) or ductal carcinoma in situ (DCIS) on pathologic examination of the targeted lesion. All patients underwent surgical resection following cryoablation. Of the 87 cancers treated with cryoablation and eligible for evaluation, central pathologic review revealed successful cryoablation in 66 (75.9 %) cancers and residual IBC and/ or DCIS in 21 (24.1 %) cancers. When multifocal disease outside of the targeted cryoablation zone was not defined as an ablation failure, 80/87 (92 %) of the treated cancers had a successful cryoablation. Successful cryoablation, as determined by the institution pathology review, was observed in 60 breasts, corresponding to a success rate of 69.0 %. Residual IBC (with or without residual DCIS) was found in 14 of 87 (16.1 %) breasts. Residual DCIS alone was found in 15 of 87 (17.2 %) breasts. A limitation of this study is the varying definitions and reported rates of 'successful cryoablation'. Comparison of long term health outcomes of cryoablation with other treatment options is lacking.

Niu et al. (2013) retrospectively studied 120 metastatic breast cancer (MBC) patients, dividing them into cryotherapy (91 patients) and chemotherapy (29 patients) groups. In the cryotherapy group, 37 patients with tumor recurrence received multiple cryoablations, while 54 patients received only a single cryoablation. Moreover, 62 cryotherapy-group patients underwent cryoablation immediately after the detection of metastases (timely cryotherapy); 35 patients received simultaneous immunotherapy (cryo-immunotherapy), and 29 patients
underwent cryoablation 3 months after receiving chemotherapy in other centers (chemo-cryoablation and delayed cryoablation). Overall survival (OS) after the diagnosis of MBC was assessed after a 10-year follow-up. The median OS was higher in the cryotherapy group (55 months) than in the chemotherapy group (27 months; \( p<0.0001 \)). In the cryotherapy group, longer median OS was associated with multiple (76 months) rather than single cryoablations (48 months; \( p=0.0005 \)) and with timely (67 months) rather than delayed cryoablation (48 months; \( p=0.0012 \)). The authors propose timely and multiple cryoablations, especially when combined with immunotherapy, may extend overall survival. This study is limited by retrospective study design.

Manenti et al. (2013) retrospectively evaluated 80 patients, 40 patients underwent cryoablation and 40 patients underwent radiofrequency ablation, both with sentinel lymph node excision. The postmenopausal women had biopsy-proven ductal invasive unifocal breast cancer 2 cm or smaller (T1), well differentiated tumor (G1 and G2) visible in both ultrasound (US) and magnetic resonance imaging (MRI) studies, and tumor located at least 1 cm from the skin and 1 cm from the chest wall at US examination. At four weeks follow up the authors concluded that there was complete necrosis of the lesion, and good cosmetic outcome and patient satisfaction achieved in most cases.

Zhau and Wu (2010) conducted a systematic review of the literature to evaluate minimally invasive thermal ablation techniques for the treatment of breast cancer. A total of 38 studies (844 patients) met the inclusion criteria. The included studies evaluated radiofrequency ablation, laser ablation, microwave ablation, and cryoablation. Most studies of cryoablation have been conducted in research settings for the evaluation of technical safety and feasibility, and have not been used alone in clinical practice. The authors noted that a number of problems with thermal ablation remain to be resolved, including a lack of ability to precisely determine tumor size, determination of 100% tumor killing, ability to follow local recurrence, and cosmetic outcome. The authors concluded that large randomized controlled studies are required to assess the long-term advantage of minimally invasive thermal ablation techniques.

Tafra et al. (2006) conducted a randomized controlled trial to compare the surgical results of cryo-assisted localization (CAL) and needle-wire localization (NWL) in 310 patients undergoing lumpectomy for breast cancer. Patients were randomized on a two to one basis to intraoperative CAL or NWL. For patients assigned to the CAL group, a cryoprobe was inserted under ultrasound guidance, an ice ball created an 8–10 mm margin around the lesion, and the palpable ice ball was dissected. For patients in the NWL group, NWL was performed according to each institution’s protocol, and standard resection was performed. Positive margin status did not differ between the two groups. The volume of tissue removed was significantly less in the CAL group (49 ml vs. 66 ml, \( p=.002 \)). Re-excision rates for positive margins were similar in both groups. CAL was superior in ease of lumpectomy, quality of specimen, acute surgical cosmesis, invasive positive margin rate (11% vs. 20%, \( p=.035 \)). CAL, however, had a higher observed ductal carcinoma in situ-positive margin rate that approached statistical significance (11% vs. 18%, \( p=.052 \)).

Studies of cryoablation for the treatment of breast cancer consist primarily of small pilot studies and feasibility studies. There is insufficient evidence to demonstrate that cryoablation of breast cancer lesions, performed in lieu of or in conjunction with lumpectomy, is equivalent to the current accepted treatment of lumpectomy (i.e., surgical removal of the tumor with confirmation of clear margins) or mastectomy (i.e., surgical removal of the breast and selected axillary lymph nodes) in terms of survival, cancer recurrence or tissue response to adjuvant therapy.

Professional Societies/Organizations

**American Society of Breast Surgeons (ASBS):** The ASBS Consensus Guideline on the Use of Transcutaneous and Percutaneous Methods for the Treatment of Benign and Malignant Tumors of the Breast (Approved June 22, 2017) included the following recommendations:

Indications for cryoablation or percutaneous excision of a fibroadenoma:

a. The lesion must be easily visualized on ultrasound.

b. The diagnosis of fibroadenoma must be confirmed histologically on core biopsy prior to treatment.

c. The diagnosis of fibroadenoma must be concordant with the imaging findings, patient history, and physical exam.
d. Lesions should be less than 4 cm in largest diameter

Indications for percutaneous and/or transcutaneous treatments (such as ablation by focused ultrasound, laser, cryotherapy, microwave, and radiofrequency) of malignant tumors of the breast:

Percutaneous and/or transcutaneous treatments of malignant tumors of the breast are not specifically approved by the FDA, though some ablative technologies are approved for treatment of benign and malignant soft tissue tumors. Therefore, ablative and percutaneous excisional treatments for breast cancer are considered investigational and should not be performed outside the realm of a clinical trial.

**National Comprehensive Cancer Network (NCCN):** Cryoablation is not included as a treatment option in current (v3.2017) NCCN breast cancer clinical practice guidelines.

**National Cancer Institute (NCI):** Cryotherapy is not mentioned as a treatment option in the Breast Cancer Treatment PDQ®, updated in 2017.

**The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative**

No relevant information.

**Use Outside of the US**

No relevant information.

### Coding/Billing Information

**Note:**

1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Considered Experimental/Investigational/Unproven:**

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<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
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<td>19105</td>
<td>Ablation, cryosurgical, of fibroadenoma, including ultrasound guidance, each fibroadenoma</td>
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<tr>
<td>19499</td>
<td>Unlisted procedure, breast</td>
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### References


