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Cryoablation of Primary Breast Cancer in Patients Ineligible for Clinical Trials: A Multiinstitutional Study

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https://doi.org/10.2214/AJR.24.31392
Accepted: June 27, 2024
Article Type: Original Research
Article Section: Breast Imaging

The complete title page, as provided by the authors, is available at the end of this article.

Abstract

Background: Breast cancer cryoablation clinical trials have strict inclusion criteria that exclude patients with potentially treatable disease.

Objective: This study's purpose was to evaluate the safety and outcomes of breast cancer cryoablation without surgical excision in patients ineligible for prospective cryoablation clinical trials due to unfavorable patient or tumor characteristics.

Methods: This retrospective study included women who underwent cryoablation of biopsy-proven unifocal primary breast cancer with locally curative intent, without surgical excision, despite being ineligible for (and thus excluded from) cryoablation clinical trials, across seven institutions between January 1, 2000 and August 26, 2021. Adverse events (AEs) were recorded. Cryoablation procedures were classified as technically successful if they were not prematurely terminated and achieved intended treatment parameters and the first imaging follow-up showed no evidence of residual disease. Results of follow-up biopsies were recorded. Ipsilateral breast tumor recurrences (IBTR) diagnosed during follow-up were identified and classified as true recurrence or new primary disease. A competing-risk model was used to estimate the cumulative incidence of IBTR accounting for death before IBTR.

Results: The final study sample included 112 patients (median age, 71 years). A total of 7/112 (6.3%) patients had a minor AE; no moderate or major AE occurred. A total of 110/112 (98.2%) cryoablation procedures were techni-

Recommended citation:
Oueidat K, Baird GL, Barclay-White B, et al. Cryoablation of Primary Breast Cancer in Patients Ineligible for Clinical Trials: A Multiinstitutional Study. *AJR* 2024 Jul 10 [published online]. Accepted manuscript. doi:10.2214/AJR.24.31392

An electronic supplement to this article is available at:
https://www.ajronline.org/doi/suppl/10.2214/AJR.24.31392/suppl_file/24_31392_suppl.pdf

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cally successful. During median follow-up of 2.0 years, 22/110 (20.0%) patients underwent biopsy for suspicious imaging findings in the ipsilateral breast, yielding benign concordant findings in 9/22 (40.9%) and IBTR in 12/22 (54.5%). Overall, 12/110 (10.9%) patients experienced IBTR, including 7 with true recurrence and 5 with new primary disease; 3/12 (25.0%) patients with IBTR had received earlier adjuvant or neoadjuvant therapy. When accounting for death as a competing risk, the cumulative incidence of IBTR was 5.3%, 12.2%, and 18.2% at 1, 2, and 3 years, respectively.

Conclusion: In select individuals with unfavorable patient or tumor characteristics, breast cancer cryoablation provides a safe alternative to surgery with good outcomes. These findings may be particularly relevant in patients who are also poor surgical candidates.

Clinical Impact: Breast cancer cryoablation can be safely applied in a larger patient population than defined by clinical trial inclusion criteria.

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Highlights

Key Findings: Among 112 patients excluded from clinical trials, breast cancer cryoablation had a frequency of technical success of 98.2% (110/112) and of AE of 6.3% (7/112); all AEs were minor. During a median follow-up of 2.0 years, 12/110 (10.9%) patients experienced IBTR (seven with true recurrence; five with new primary disease).

Importance: In select individuals with unfavorable patient or tumor characteristics, breast cancer cryoablation provides a safe alternative to surgery that achieves good outcomes.

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Introduction

Ultrasound-guided cryoablation is a safe, effective, and minimally invasive outpatient procedure used to treat breast cancer. It uses lethally cold temperatures to induce tissue necrosis and cell death [1]. Benefits of cryoablation compared to surgery include [2,3]: use of local anesthesia without sedation or general anesthesia; shorter recovery times; improved cosmesis and patient satisfaction; and decreased cost. Cryoablation may be particularly beneficial in patients considered poor surgical candidates due to comorbidities. A recent review outlined tips for implementing and sustaining a breast cryoablation service line in practice [4].

Prospective clinical trials (e.g., ACOSOG Z1072 and ICE3) have evaluated the procedural efficacy of cryoablation for breast cancer treatment. These trials have had strict inclusion criteria, enrolling only patients with patient and tumor characteristics associated with favorable cryoablation response [5,6]. These criteria have included: female sex; age of at least 50 years; early-stage, low-risk, unifocal invasive ductal carcinoma (IDC) measuring less than 1.5 cm; no extensive intraductal component (EIC); Nottingham grade 1 or 2 of 3; low Ki-67 proliferation index; hormonal receptor status of estrogen receptor (ER) positive, progesterone receptor (PR) positive, and HER2 negative; clinically node negative; and no evidence of distant metastatic disease. Additionally, the inclusion criteria have indicated that the tumor should be well visualized on ultrasound and be located at least 0.5 cm from the overlying skin and at least 0.3 cm from the underlying pectoralis muscle. Moreover, the inclusion criteria have indicated that trial candidates must be able to tolerate and receive adjuvant therapy.

Results from the aforementioned trials have demonstrated that cryoablation is a safe and efficacious alternative to surgery for breast cancer treatment in this restricted patient population. However, data remain lacking regarding breast cancer cryoablation in trial-ineligible patients, who may have potentially treatable disease despite being less optimal candidates for such therapy. This study's aim was to evaluate the safety and outcomes of breast cancer cryoablation without surgical excision in patients ineligible for prospective cryoablation clinical trials due to unfavorable patient or tumor characteristics.

Methods

Patients

This HIPAA-compliant retrospective study was performed at seven institutions. The study was approved by each institution's institutional review board, all of which waived the requirement for informed consent.

The PACS and EHR of each institution was reviewed to identify female patients with biopsy-proven primary breast cancer treated by cryoablation without surgical excision outside of a clinical trial between January 1, 2000 and August 26, 2021. Patients were then excluded if they would have been eligible for past and ongoing prospective clinical trials and underwent cryoablation outside of trials only because of non-cancer-related reasons. Additional patients

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were excluded for the following reasons: cryoablation lacked locally curative intent; multifocal or multicentric disease (due to ambiguity in determining study outcomes in such patients); no postablation imaging follow-up performed within the study period (due to inability to assess for procedural technical success in such patients). The remaining patients represented the final sample of patients who underwent breast cancer cryoablation despite being ineligible for, and thus excluded from, clinical trials. Patients with nodal or distant metastatic disease were eligible for inclusion in the present study if the cryoablation was performed with locally curative intent despite the presence of metastatic disease. Patients generally underwent cryoablation because of patient preference.

Cryoablation Procedures

Cryoablation was performed under ultrasound guidance in the outpatient setting. A single fellowship-trained radiologist performed all cryoablations at each of the seven institutions. Thus, the procedures were performed by seven different radiologists, including four breast radiologists, two breast and interventional radiologists, and one interventional radiologist, with 1-25 years of posttraining experience. All procedures were performed using local anesthesia, without sedation. Procedures were performed using a cryoablation device with liquid nitrogen [Visica 2 Treatment System (Sanarus Technologies Inc., Pleasanton, CA, USA), ProSense Cryosurgical System (IceCure Medical Ltd., Caesarea, Israel)] or a cryoablation device with high-pressure argon gas [Visual-ICE Cryoablation System (Boston Scientific, Marlborough, MA, USA), and Cryocare SL Surgical System (Varian Medical Systems Inc., Palo Alto, CA, USA)]. Selection of a particular cryoablation device generally depended on institutional availability, physician preference, and lesion considerations.

The proceduralist determined cryoablation needle selection and placement, with the intent to ablate the entirety of the targeted lesion with lethally cold temperatures. The proceduralist aimed to center the lesion within the ice and to expand the ice ball such that the ultrasound-visible ice margin was estimated to be located at least 0.5-1.0 cm beyond all tumor margins based upon long- and short-axis measurements of both the ice and tumor. Each procedure consisted of two freeze-thaw cycles, typically including 5-10-minute freezes with an intervening 5-10-minute passive thaw. Following the second freeze, a 1.5-minute active thaw was typically performed, to remove the needle before the ice ball melted over the following 15-20 minutes. Saline hydrodisplacement and heating pads were used as needed to protect the skin from cold-induced injury.

At the time of cryoablations, the proceduralists documented adverse events (AE) and classified these events using the Common Terminology Criteria for Adverse Events 5.0 as grade 1 (mild), 2 (moderate), or 3 (severe) [7].

Pre-ablation and post-ablation imaging protocols varied depending on institutional availability, proceduralist preference, and patient characteristics. All patients underwent pre-ablation imaging by mammography and ultrasound; patients may have also undergone pre-ablation contrast-enhanced breast MRI. All patients underwent imaging follow-up after cryoablation by a

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variable combination of mammography, ultrasound, and MRI. Some institutions also used CT or FDG PET/CT as follow-up modalities. The initial follow-up imaging was generally reported as showing no evidence of recurrent disease if the targeted lesion was satisfactorily centered within a larger mature ablation zone based on anatomic landmarks (e.g., the biopsy marking clip placed in the targeted lesion at the time of initial histologic confirmation). Biopsy was generally recommended for suspicious findings detected in the ipsilateral breast on follow-up imaging [8]. The administration of adjuvant therapies after cryoablation depended on local tumor board recommendations and patient preference.

Data Extraction

At each institution, the radiologist who performed the cryoablation procedures reviewed all available medical and imaging records for each patient to extract the following baseline patient and tumor characteristics: age; presence of comorbidities; purpose of preablation imaging (screening vs diagnostic); presence of a palpable lesion; tumor laterality; performance of preablation MRI or of FDG PET/CT in addition to mammography and ultrasound; the tumor's clockface location on ultrasound (upper outer quadrant vs other location); the largest tumor dimension on ultrasound; the tumor distance on ultrasound from the nipple, skin, and pectoralis; presence of a greater tumor size on MRI than on ultrasound; the maximum tumor size on MRI; the tumor distance on MRI from the pectoralis; and presence of nodal or distant metastatic disease [9]. The MRI-related features were only assessed in patients who underwent preablation MRI. The following baseline pathologic features were also recorded for each tumor: histologic diagnosis; presence of a ductal carcinoma in situ (DCIS) component; the DCIS percentage (for tumors with a DCIS component); Nottingham grade; and hormone receptor status. Additionally, reasons why patients were ineligible for cryoablation trials were recorded, with potential recording of multiple reasons per patient. Features of cryoablation procedures were recorded, including the interval between preablation lesion biopsy and cryoablation; the cryoablation device used; the reason for selecting the given device (for procedures performed using a Boston Scientific device); the number of probes used (for procedures performed using a Boston Scientific or Varian device); the first freeze duration; the passive thaw duration; the second freeze duration; the total freeze duration; the maximum long- and short-axis dimensions of the ice ball; and the use and volume of intraprocedural hydrodisplacement. Types of neoadjuvant and adjuvant therapy received were recorded. Furthermore, the radiologist recorded whether an AE occurred; for each AE, the grade, symptoms, subsequent management, and associated outcome were also recorded.

For purposes of the present investigation, the radiologists also classified the first attempted cryoablation procedure in each patient as a technical success or failure. The procedure was classified as a technical success if it was not prematurely terminated for any reason, it was reported as achieving the intended treatment parameters for the targeted lesion, and the first imaging follow-up was reported as showing no evidence of residual disease. Details of technical failures were recorded.

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Outcomes

The outcomes analysis was performed in patients in whom the initially attempted cryoablation procedure was classified as a technical success. At each institution, the radiologist who performed the cryoablation procedures reviewed all available medical and imaging records through August 26, 2021, to determine the study outcomes.

For each patient, the radiologist recorded the time interval from cryoablation to the first imaging follow-up, the time points at follow-up imaging was performed, and the total time of postablation follow-up. The radiologist also recorded whether each patient was recommended to undergo biopsy of suspicious findings detected on follow-up imaging in the breast ipsilateral to the cryoablation; the follow-up times for such recommendations were recorded. The radiologist additionally recorded whether such patients underwent the recommended biopsies and performed biopsies' histologic outcomes.

All instances of ipsilateral breast tumor recurrence (IBTR) histologically confirmed by biopsy were recorded. Each IBTR was classified as true recurrence (i.e., regrowth of disease at the tumor bed) or new primary disease (i.e., disease distinct from the index lesion in histology and/or location) [10]. Additional data recorded for each IBTR included presence of a suspicious finding on follow-up imaging; interval between cryoablation and IBTR diagnosis; pathologic details of the IBTR (histology, grade, and hormone receptor status); subsequent management; and follow-up duration and disease status after such management.

The radiologists also reviewed the available records to identify documentation of death. In patients who died, the time interval from cryoablation to death was recorded. In patients without documentation of death, the time interval from cryoablation to the last documented medical encounter was recorded as a measure of survival. All deaths were classified as cancer-related or non-cancer-related.

Statistical Analysis

Data were summarized using standard descriptive statistics. PPV2 and PPV3 were calculated as the percentage of patients recommended to undergo biopsy, and the percentage of patients who underwent biopsy, respectively, in whom biopsy diagnosed IBTR. For these calculations, patients who underwent biopsy and in whom biopsy results were unavailable were classified as not having IBTR. Kaplan-Meier curves analysis was used to estimate during follow-up the likelihood of IBTR or death; the likelihood of IBTR when censoring for death; the cumulative incidence of IBTR when accounting for death before IBTR as a competing risk; and the likelihood of death. These outcomes were each reported at time points of 1, 2, and 3 years, along with standard errors (SE). The IBTR models censored patients at the time of their last follow-up imaging in the absence of other events. The assessment of IBTR when accounting for death as a competing risk used the method of Fine and Grey [11]; this model was confirmed to satisfy the Supremum test for proportional hazards assumption, the Schoenfeld test for

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proportion hazard assumption, and the goodness-of-fit test for proportional subdistribution hazard, all assessed at a p-value threshold of greater than .20. The 95% confidence limits were derived for the likelihood estimates. Analyses were performed by a statistician (GB, 11 years of experience). Analyses were conducted using SAS Software 9.4 (SAS Inc, Cary, NC), including the LIFETEST and PHREG procedures for outcome assessments.

Results

Patient Selection

The initial search identified 144 patients with primary breast cancer treated by 144 cryoablation procedures outside of clinical trials at the seven institutions during the study period. Ten patients were excluded because they would have been eligible for prospective clinical trials and underwent cryoablation outside of trials only because of non-cancer-related reasons. Of the remaining 134 patients, two were excluded because they did not undergo cryoablation with locally curative intent but rather with palliative intent to debulk a large tumor and reduce symptom; seven were excluded because they had multifocal (n=6) or multicentric (n=1) disease; and 13 were excluded because they had no imaging follow-up before the end of the study period. Thus, the final sample included 112 patients who underwent cryoablation of unifocal breast cancer with locally curative intent, with at least one imaging follow-up during the study interval (Figure 1).

Patient and Tumor Characteristics

Table 1 summarizes baseline patient and tumor characteristics. The median patient age at the time of cryoablation was 71 years (IQR, 62-79 years). A total of 60/112 (53.6%) patients had at least one comorbidity. The median largest tumor dimension on ultrasound was 1.0 cm (IQR, 0.7-1.8 cm). Tumors' median distance on ultrasound to the nipple, skin, and pectoralis were 5.0 cm (IQR, 3-7 cm), 0.7 cm (IQR, 0.5-1.1 cm) and 0.6 cm (IQR, 0.4-1.1cm), respectively. Five (4.5%) patients had N1 nodal and/or distant metastatic disease at the time of cryoablation. Of the 112 tumors, 88 (78.6%) were IDC not otherwise specified (NOS). Of these 88 IDCs, 32 (28.6%) had a DCIS component; the DCIS percentage was reported in 22 IDCs and had a median value of 17.5% (IQR, 5.0-25.0%). Additional histologic diagnoses included invasive lobular carcinoma (ILC), DCIS, mucinous carcinoma, papillary carcinoma, and tubular carcinoma. Tumors were assessed as grade 1 in 61 (54.5%), grade 2 in 40 (35.7%), and grade 3 in 11 (9.8%). The hormone receptor status was ER+, PR+, HER2- in 87 (77.7%), and triple-negative in 10 (8.9%).

Table 2 summarizes reasons why patients were ineligible for cryoablation clinical trials. The most common reasons why patients were ineligible for cryoablation clinical trials were a largest lesion dimension on ultrasound or MRI greater than 1.5 cm (n=40), patient request not to undergo or inability to tolerate adjuvant therapy (n=36), and tumor histology other than IDC (n=32).

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Table 3 summarizes adjuvant and neoadjuvant treatments received. A total of 35/112 (31.3%) patients received some form of adjuvant therapy after cryoablation. A total of 72/112 (64.3%) patients underwent cryoablation without any form of adjuvant or neoadjuvant treatment.

Cryoablation Procedures

Table 4 summarizes details of cryoablation procedures. The median time between preablation lesion biopsy and cryoablation was 49.5 days (IQR, 36-100 days). The most commonly used cryoablation device was Sanarus Visica 2 (80/112, 71.4%). Fifteen procedures used a Boston Scientific device. This device was selected because of institutional availability in 5 patients, physician preference in 4 patients, small lesion size in 3 patients, and the need for multiple probes for complete lesion treatment in 3 patients. All procedures using a Boston Scientific device used at least two probes.

The median duration of total freeze time was 14 minutes (IQR, 12-16 min). The median long-axis and short-axis diameters of the maximum ice ball formed during treatment were 5.0 cm (IQR, 4.4-5.5 cm) and 3.6 cm (IQR, 3.0-4.0 cm), respectively. Intraprocedural hydrodisplacement was used in 104 (92.9%) procedures. The hydrodisplacement volume was recorded in 97 of these procedures and had a median value of 50 mL (IQR, 30-100 mL). Figure 2 shows typical intraprocedural ultrasound findings.

A total of 7/112 (6.3%) procedures had an associated AE. All AEs were assessed as grade 1 (mild) and involved hypothermia-induced skin damage, encompassing varying combinations of erythema, induration, blistering, bruising, ulceration, superficial thermal burns, and nipple and skin retraction. These AEs were managed conservatively using varying combinations of warm heating pads, silver sulfadiazine cream, and topical antibiotics, with subsequent resolution. No patient experienced a moderate or severe AE.

The frequency of procedural technical success was 98.2% (110/112). Two procedures were classified as treatment failures. One of these patients developed a large superficial hematoma during lesion biopsy performed 2 weeks before ablation. At the time of ablation, the hematoma caused rapid ice propagation toward the skin, resulting in premature cryoablation termination in order to prevent hypothermic skin injury. In the other patient, the cryoablation procedure was terminated prematurely due to insufficient availability of liquid nitrogen; this patient subsequently underwent a repeat cryoablation procedure. No procedure was classified as a technical failure due to evidence of residual disease on the first imaging follow-up.

Outcomes

Outcomes were assessed in the 110 patients in whom the cryoablation procedure was classified as a technical success. The median time from cryoablation to the first imaging follow-up was 76

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days (IQR, 33-106 days). The median total follow-up duration was 2.0 years (95% CI: 1.7, 2.2 years). The maximum total follow-up duration was 5.4 years. Figure S1 shows a patient in whom postablation follow-up imaging yielded expected findings, without evidence of residual or recurrent disease.

A total of 25/110 (22.7%) patients were recommended to undergo biopsy of suspicious findings in the ipsilateral breast on a follow-up mammogram (n=12) or MRI (n=13) performed at a median follow-up of 16 months (IQR, 6-26 months). A total of 22/110 (20.0%) patients underwent a recommended biopsy of suspicious findings; three patients declined to undergo recommended biopsy. A total of 12/22 (54.5%) biopsies yielded IBTR, and 9/22 (40.9%) biopsies yielded benign concordant findings (fat necrosis [n=6], fibrocystic change [n=3]); in the remaining patient who underwent biopsy, the biopsy results were unavailable. Overall, the PPV2 was 12/25 (48.0%), and the PPV3 was 12/22 (54.5%). The PPV2 and PPV3 were 7/12 (58.3%) and 7/11 (63.6%) for follow-up mammography examinations, and 5/13 (38.5%) and 5/11 (45.5%) for follow-up MRI examinations, respectively. Figure 3 shows a representative patient with follow-up imaging showing suspicious findings that were diagnosed as IBTR on biopsy. Figure 4 shows a representative patient with follow-up imaging showing suspicious findings diagnosed as fat necrosis on biopsy.

The fraction of patients diagnosed with IBTR was 10.9% (12/110). Table 5 summarizes the characteristics and management of patients with IBTR. In these 12 patients, the median greatest dimension on ultrasound of the originally treated lesion was 1.0 cm (IQR, 0.7-1.7 cm). The hormonal receptor status of the originally treated tumor was ER+, PR+, HER2- in 11 patients and ER+, PR-, HER2- in one patient. A total of 7/12 (58.3%) IBTRs were true recurrence, and 5/12 (41.7%) were new primary disease. All 12 IBTRs showed a suspicious finding on a follow-up ultrasound examination. Eight recurrences were IDC (one with a DCIS component), one was ILC, two were DCIS, and one had unavailable histology. A total of 3/12 (25.0%) patients with IBTR, including 2/7 (28.6%) patients with true recurrence and 1/5 (20.0%) patients with new primary disease, had received adjuvant or neoadjuvant therapy before IBTR. Four patients with IBTR underwent a repeat cryoablation and remained disease-free at a median imaging follow-up after repeat cryoablation of 10 months (IQR, 3.8-17.5 months). Two patients with IBTR underwent surgical excision of the recurrence, and three patients with IBTR underwent mastectomy. Three patients with IBTR were lost to further follow-up before they underwent treatment for the recurrence.

A total of 7/110 patients died during follow-up, including one patient with a cancer-related death and six patients with a non-cancer-related death. One of the seven patients who died also had IBTR; this patient had a non-cancer-related death. The likelihood of IBTR or death was 10.4% (SE=0.03%) at 1.0 year, 17.3% (SE=0.04%) at 2.0 years, and 24.8% (SE=0.06) at 3.0 years (Fig. 5A). When censoring for death, the likelihood of IBTR was 5.4% (SE=0.02%) at 1.0 year, 12.8% (SE=0.04%) at 2.0 years, and 19.4% (SE=0.06) at 3.0 years. When accounting for death as a competing risk, the cumulative incidence of IBTR was 5.3% (SE=0.02) at 1.0 year, 12.2% (SE=0.04) at 2.0 years, and 18.2% (SE=0.06) at 3.0 years (Fig. 5B). The likelihood of death was

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3.3% (SE=0.02) at 1.0 years, 6.9% (SE=0.03) at 2.0 years, and 19.9% (SE=0.09) at 3.0 years (Fig. 5C).

Discussion

This multi-institutional study represents, to our knowledge, the largest study of breast cancer cryoablation in women who were ineligible for clinical trials due to the presence of at least one unfavorable patient or tumor characteristic in terms of the likelihood of ablation success. Of these patients, 54.3% had at least one comorbidity. A total of 6.3% of cryoablation procedures were associated with an AE, all of which were mild and resolved with conservative management. A total of 98.2% of procedures were technically successful. During a median of 2.0 years of imaging follow-up, 10.9% of patients experienced IBTR. The findings indicate the potential to safely use breast cancer cryoablation in larger patient populations than defined by clinical trial criteria.

Prior single- and multi-center studies have reported high rates of cryoablation success (up to 100%) in patients with favorable characteristics [5,6,12–15]. Historically, one of the most frequently cited reasons for technical failure is incorrect placement of a single cryoablation probe [5,12,13,16]. Other reported reasons for technical failure include high tumor grade [5], large lesion size (usually >1 cm) [5,14], and presence of a DCIS component [14,15]. Multiple additional studies and systematic reviews have confirmed these observations [17–19]. This study's frequency of procedural technical success of 98.2% is comparable to values reported in prior literature. Both technical failures in this study were due to premature procedure termination. The observed high frequency of technical success may reflect the steps taken by the proceduralists to achieve complete coverage of the targeted lesions. In contrast, positive margins have been reported in up to 40% of patients who undergo breast-conserving surgery for breast cancer, with up to 60% of patients undergoing breast-conserving surgery subsequently requiring re-excision [20].

Available literature reports variable rates of IBTR after cryoablation [5,6,18]. Prior prospective cryoablation studies were designed to demonstrate efficacy, enrolling only patients with favorable characteristics (i.e., early-stage low-grade breast cancers). Accordingly, IBTR rates were found to be similar to those observed after breast-conserving surgery, ranging from 0% to 10% at 10-year follow-up [2]. In 2021, the ICE3 trial reported an IBTR rate of 2.06% (4/194) during a mean follow-up of 34.83 months [6], lower than the present study's reported frequency. Moreover, in the present study, when accounting for death as a competing risk, the cumulative incidence of IBTR was 12.2% at 2 years and 18.2% at 3 years. Several reasons may explain the present study's higher frequency of IBTR. First, each patient had at least one unfavorable patient or tumor characteristic that resulted in their being a suboptimal candidate for cryoablation based on clinical trial inclusion criteria. Second, the determination of cryoablation technical success included the use of imaging, rather than histologic evaluation, to assess for evidence of residual disease; this approach may have caused underestimation of the frequency

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of residual disease. Specifically, residual viable tumor cells within or near the ablation zone may have been occult on initial imaging follow-up, becoming evident only on subsequent imaging, resulting in the patient being classified as having IBTR rather than being classified as having undergone a technically unsuccessful cryoablation procedure. Third, imaging may underestimate the extent of ILC, DCIS, and EIC associated with IDC, potentially leading to incomplete eradication of imaging-occult tumor located outside of the area targeted for ablation. Fourth, the median largest dimension on ultrasound of the ablated tumor was 1.0 cm, larger than the corresponding size of 0.8 cm reported in the ICE3 trial. Finally, the proceduralists had variable experience and used variable cryoablation equipment, possibly contributing to occurrences of IBTR.

During post-ablation surveillance, 22.7% of patients were recommended to undergo biopsy due to suspicious imaging findings. A total of 54.5% of biopsies yielded IBTR, and 40.9% yielded concordant benign findings, most commonly fat necrosis (a recognized common false-positive finding on postablation follow-up imaging) [8]. The instances of IBTR included both true recurrence and new primary disease. A diagnosis of true recurrence suggests failed cryoablation due to incomplete ablation, with the presence of residual disease that may not have been appreciated at the time of imaging workup and procedural targeting. On the other hand, new primary disease (i.e., disease distinct from the index lesion in histology and/or location) may relate to ineffective adjuvant medical and radiation therapy. Some form of adjuvant therapy was received by only 31.3% of patients in this study, versus by all patients in clinical trials. Studies of breast-conservation therapy [21,22] or of cryoablation [2] have found adjuvant therapy to be associated with lower rates of IBTR.

In this study, the PPV2 and PPV3 for detection of IBTR after cryoablation were lower for MRI than for mammography. The lower PPV for MRI may reflect false-positive interpretations due to enhancement from postablation inflammatory change or fat necrosis. However, fat necrosis may also cause false-positive interpretations on conventional mammography. Although not evaluated in the present study, contrast-enhanced mammography represents an additional promising imaging modality for post-cryoablation follow-up, with potential advantages including improved PPV, reduced time and cost, increased eligibility, and increased accessibility compared to MRI [23]. Biopsy recommendations may also be reduced through multimodality imaging approaches. Future studies should seek to optimize postablation imaging follow-up algorithms, including investigation of newer imaging modalities and agents, such as ^{18}F-fluorestradiol PET/CT in patients with hormone-receptor positive breast cancers [24].

The frequency of AEs was low, and no moderate or severe AE occurred. These findings align with a systematic review of ablation techniques for breast cancer treatment that reported frequencies of minor and major AEs after cryoablation of 18% and 2%, respectively [25]. Although these frequencies vary across studies, the frequency and severity of AEs are overall favorable after cryoablation in comparison with results for radiotherapy or surgery [26,27].

An advantage of cryoablation is the ability to perform repeat procedures [18]. In this study, one patient underwent a repeat ablation after a first attempted cryoablation was technically

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unsuccessful. Four additional patients underwent repeat cryoablation to treat recurrence and remained disease-free during the remainder of the study period (median, 10 months).

This study had limitations. First, it was retrospective. Second, its multi-institutional design yielded various sources of heterogeneity that could limit the findings' generalizability. Such heterogeneity includes proceduralist experience, follow-up imaging protocols (including imaging frequency and modality selection), and use of adjuvant therapies. Third, as previously noted, technical success was assessed on imaging and not by histologic evaluation; after ablation, biopsy was only performed to evaluate suspicious imaging findings. Fourth, outcomes were not directly compared between cryoablation and other treatments. Lastly, the median follow-up period was short at 2.0 years.

Conclusion

In patients with breast cancer who underwent cryoablation with locally curative intent despite being ineligible for cryoablation clinical trials, such treatment had a low frequency of AEs and a high frequency of procedural technical success. The frequency of IBTR was higher than previously reported for prospective clinical trials. Nonetheless, in select individuals with unfavorable patient or tumor characteristics, cryoablation remains a safe alternative to surgery that has overall good outcomes. These findings may be particularly relevant in patients who are also poor surgical candidates due to comorbidities.

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Tables

Table 1. Baseline patient and tumor characteristics

Characteristic	Value **(n=112[a])**
Study institution	
1	26 (23.2)
2	7 (6.3)
3	5 (4.5)
4	4 (3.6)
5	34 (30.4)
6	33 (29.5)
7	3 (2.7)
Age (y), median (IQR)	71 (62-79)
Comorbidities, n (%)	
Cardiovascular disease[b]	41 (36.6)
Lung disease[c]	13 (11.6)
Non-breast primary cancer	11 (9.8)
Diabetes mellitus	10 (8.9)
Liver disease[d]	3 (2.7)
Dementia or mild cognitive impairment	3 (2.7)
Neurologic disorder (other than dementia or mild cognitive impairment)[e]	5 (4.5)
Thyroid disorder[f]	8 (7.1)
Chronic kidney disease	4 (3.6)
At least one comorbidity	60 (53.6)
Purpose of pre-procedure imaging, n (%)	
Screening	88 (78.6)
Diagnostic	24 (21.4)
Palpable lesion, n (%)	32 (28.6)
Laterality, n (%)	
Right breast	51 (45.5)
Left Breast	61 (54.5)
Pre-procedure imaging[g], n (%)	
MRI	68 (60.7)
FDG PET/CT	6 (5.4)
Ultrasound clockface location	
Upper outer quadrant, n (%)	67 (59.8)
Other, n (%)	45 (40.2)
Greatest lesion diameter on ultrasound (cm), median (IQR)	1 (0.7-1.83)
Lesion distance on ultrasound from nipple (cm), median (IQR)	5 (3-7)
Lesion distance on ultrasound from skin (cm), median (IQR)	0.7 (0.5-1.1)
Lesion distance on ultrasound from pectoralis (cm), median (IQR)	0.6 (0.4-1.1)
Greater lesion size on MRI than ultrasound[h], n (%)	17 (15.2)
Greatest lesion dimension on MRI (cm)[h], median (IQR)	1.6 (1.3-2.3)
Lesion distance on MRI from pectoralis (cm)[h], median (IQR)	1.05 (0.6-3)
Presence of N1 nodal and/or distant metastatic disease, n (%)	5 (4.5)
N1 nodal disease	4 (3.6)
Distant metastatic disease	1 (0.9)
Histologic diagnosis, n (%)	
IDC NOS	88 (78.6)
ILC	9 (8.0)
DCIS	8 (7.1)
Mucinous carcinoma	2 (1.8)
Papillary carcinoma	4 (3.6)
Tubular carcinoma	1 (0.9)
DCIS component, n (%)	32 (28.6)
DCIS percentage[i], median (IQR)	17.5 (5-25)

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Nottingham grade, n (%)	
1	61 (54.5)
2	40 (35.7)
3	11 (9.8)
Hormone receptor status	
ER+, PR+, HER2-	87 (77.7)
ER+, PR+, HER2+	4 (3.6)
ER+, PR-, HER2-	9 (8.0)
Triple negative	10 (8.9)

[a]Unless otherwise indicated

[b]Includes hypertension, heart failure, coronary artery disease, and atrial fibrillation

[c]Includes chronic obstructive pulmonary disease and pulmonary fibrosis

[d]Includes cirrhosis, primary sclerosing cholangitis, and primary biliary cholangitis

[e]Includes stroke and multiple sclerosis

[f]Includes hypothyroidism, hyperthyroidism, and thyroiditis

[g]In addition to mammography and ultrasound

[h]Reported only among patients who underwent MRI before ablation

[i]Reported only among patients with a DCIS component

invasive ductal carcinoma (IDC), not otherwise specified (NOS), invasive lobular carcinoma (ILC), ductal carcinoma in situ (DCIS), estrogen receptor (ER), progesterone receptor (PR)

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Table 2. Reasons why patients were ineligible for cryoablation clinical trials s

Reason	Value (n=112)
Age < 50 years old	7 (6.25)
Greatest lesion dimension on ultrasound or MRI > 1.5 cm	40 (35.7)
Lesion distance on ultrasound from skin < 0.5 cm	27 (24.11)
Lesion distance on ultrasound from pectoralis < 0.3 cm	19 (17.0)
Histology other than IDC	32 (28.6)
In patient with IDC, presence of EID (defined as ≥ 25% DCIS component)	9 (8.0)
Hormone receptor status not ER+, PR+, HER2-	24 (21.4)
Nottingham grade 3	11 (9.8)
High proliferation marker (defined as Ki-67 > 14%)	1 (0.9)
Presence of distant metastatic disease	2 (1.8)
Prior or concurrent neoadjuvant therapy	3 (2.7)
Patient request not to undergo, or inability to tolerate, adjuvant therapy	36 (32.1)
Inability to tolerate MRI	15 (13.4)
Funding issue	9 (8.0)
No ongoing trial	1 (0.9)
Other cancer-related reason	7 (6.3)

Data expressed as count with percentage in parentheses.

[a]Patients were potentially ineligible for multiple reasons.

invasive ductal carcinoma (IDC), extensive intraductal component (EIC), ductal carcinoma in situ (DCIS), estrogen receptor (ER), progesterone receptor (PR)

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Table 3. Details of cryoablation procedures

Variable	Value (N=112)
Days between biopsy and cryoablation, median (IQR)	46.5 (34-99)
Cryoablation device, n (%)	
Sanarus Visica 2 (liquid nitrogen)	80 (71.4)
IceCure Medical (liquid nitrogen)	16 (14.3)
Varian (argon)	1 (0.9)
Boston Scientific (argon)	15 (13.4)
Reason for selecting a Boston Scientific cryoablation device (n)	
Institutional availability	5
Physician preference	4
Small lesion size	3
Need for multiple probes for complete lesion treatment	3
Number of probes used[a] (n)	
1	4
2	7
3	4
4	1
First freeze duration (minutes), median (IQR)	7 (6-8)
Passive thaw duration (minutes), median (IQR)	10 (8-10)
Second freeze duration (minutes), median (IQR)	6 (6-8)
Total freeze time duration (minutes), median (IQR)	14 (12-16)
Maximum ice ball dimension (cm), median (IQR)	
Long axis	5 (4.4-5.5)
Short axis	3.6 (3-4)
Intraprocedural hydrodisplacement used, n (%)	104 (92.9)
Intraprocedural hydrodisplacement volume[b] (mL), median (IQR)	50 (30-100)
Adverse events[c], n (%)	7 (6.3)

[a]Reported only for procedures performed using a Boston Scientific or Varian device
[b]Reported only for procedures that used hydrodisplacement
[c]All seven adverse events were grade 1 and comprised hypothermia-induced skin damage, encompassing varying combinations of erythema, induration, blistering, bruising, ulceration, superficial thermal burns, and nipple and skin retraction. Additionally, all adverse events were managed conservatively by varying combinations of warm heating pads, liquid silver gel, and topical antibiotics, with subsequent resolution

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Table 4. Types of neoadjuvant and adjuvant therapy received

Variable	Value (N=112)
Neoadjuvant endocrine therapy and adjuvant endocrine therapy	1 (0.9)
Neoadjuvant chemotherapy and adjuvant chemotherapy	2 (1.8)
Neoadjuvant chemotherapy	2 (1.8)
Neoadjuvant chemotherapy, adjuvant endocrine therapy, adjuvant chemotherapy, and adjuvant radiation therapy	1 (0.9)
Adjuvant endocrine therapy	23 (20.5)
Adjuvant endocrine therapy and adjuvant radiation therapy	8 (7.1)
None	72 (64.3)
Unknown	3 (2.7)

Data expressed as count with percentage in parentheses

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Table 5. Cancer characteristics and management for patients diagnosed with IBTR after breast cancer cryoablation.

Patient	Age at Time of Ablation (y)	Comorbidities	Treated Lesion's Greatest Dimension on Baseline Ultrasound (cm)	Hormone Receptor Status of Treated Tumor	Reason(s) for Trial Ineligibility	Total Freeze Time (min)	Maximum Ice Ball Dimension (Long Axis) (cm)	Maximum Ice Ball Dimension (Short Axis) (cm)	Adjuvant/ Neoadjuvant Therapy Received	Time Between Ablation and IBTR Diagnosis (mo)	Pathology of IBTR	Subsequent Management
1 (New primary disease)	66	Lung disease, diabetes mellitus, cirrhosis	0.8	ER+/PR+/HER2-	Lesion < 0.3 cm from pectoralis	8	5.5	3.2	None	4	ILC, grade 2, ER+/PR+/HER2-	Repeat cryoablation
2 (New primary disease)	63	Lung disease, cirrhosis	1.8	ER+/PR+/HER2-	Lesion > 1.5 cm in size; lesion < 0.5 cm from skin; lesion < 0.3 cm from pectoralis	16	3.5	2.9	Adjuvant endocrine therapy	6	IDC, grade 2, ER+/PR+/HER2-	Repeat cryoablation
3 (New primary disease)	76	None	0.7	ER+/PR+/HER2-	Lesion < 0.3 cm from pectoralis; histology other than IDC (encapsulated papillary carcinoma with no invasive component); tumor with ≥ 25% DCIS component	12	3.8	3.0	None	17	IDC with DCIS component, grade 1, ER+/PR+/HER2-	Surgical excision recommended; patient lost to follow-up
4 (New primary disease)	67	None	0.6	ER+/PR+/HER2-	Lesion < 0.5 cm from skin; lesion < 0.3 cm from pectorals; patient declined to undergo or could not tolerate adjuvant therapy	14	3.7	2.9	None	26	DCIS, grade 3, ER+/PR+/HER2-	Mastectomy
5 (New primary disease)	60	None	0.4	ER+/PR+/HER2-	Patient declined to undergo or could not tolerate adjuvant therapy	12	4.9	3.6	None	12	IDC, grade 2, ER+/PR+/HER2-	Mastectomy
6 (True recurrence)	89	CVD	1.9	ER+/PR+/HER2-	Lesion > 1.5 cm in size; lesion < 0.5 cm from skin; lesion < 0.3 cm from pectoralis	12	4.5	3.6	Neoadjuvant chemotherapy	16	IDC, grade 2, ER+/PR+/HER2-	Standard-of-care management recommended; patient lost to follow-up
7 (True recurrence)	76	None	1.6	ER+/PR-/HER2-	Lesion > 1.5 cm in size; hormone receptor status not ER+/PR+/HER2; Nottingham grade 3	10	4.4	4.0	None	12	Histology not available, grade not available, ER+ (not evaluated for other receptors)	Repeat cryoablation
8 (True recurrence)	76	CVD, dementia	0.5	ER+/PR+/HER2-	Patient declined to undergo or could not tolerate adjuvant therapy	16	4.0	3.5	None	41	IDC, grade 2, ER+/PR+/HER2-	Repeat cryoablation
9 (True recurrence)	44	None	1.3	ER+/PR+/HER2-	Age < 50; lesion < 0.5 cm from skin; patient declined to undergo or could not tolerate adjuvant therapy	12	4.6	3.4	None	17	IDC, grade 2, ER+/PR+/HER2+	Mastectomy
10 (True recurrence)	77	None	2.2	ER+/PR+/HER2-	Lesion > 1.5 cm in size; lesion < 0.5 cm from skin; patient declined to undergo or could	16	5.3	4.3	None	13	DCIS, grade 3, ER+ (not evaluated for other receptors)	Mastectomy recommended; patient lost to follow-up

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					not tolerate adjuvant therapy							
11 (True recurrence)	80	CVD, hypothyroidism	1.13	ER+/PR+/HER2-	Histology other than IDC; patient could not tolerate MRI	16	6.3	5.7	Adjuvant endocrine therapy	25	IDC, grade 2, ER+/PR+/HER2-	Surgical excision
12 (True recurrence)	51	None	0.9	ER+/PR+/HER2-	Patient declined to undergo or could not tolerate adjuvant therapy	12	5.4	3.8	None	23	IDC, grade 2, ER+/PR+/HER2-	Surgical excision

CVD = cardiovascular disease; IDC = invasive ductal carcinoma; DCIS = ductal carcinoma in situ; ILC = invasive lobular carcinoma; ER = estrogen receptor; PR = progesterone receptor

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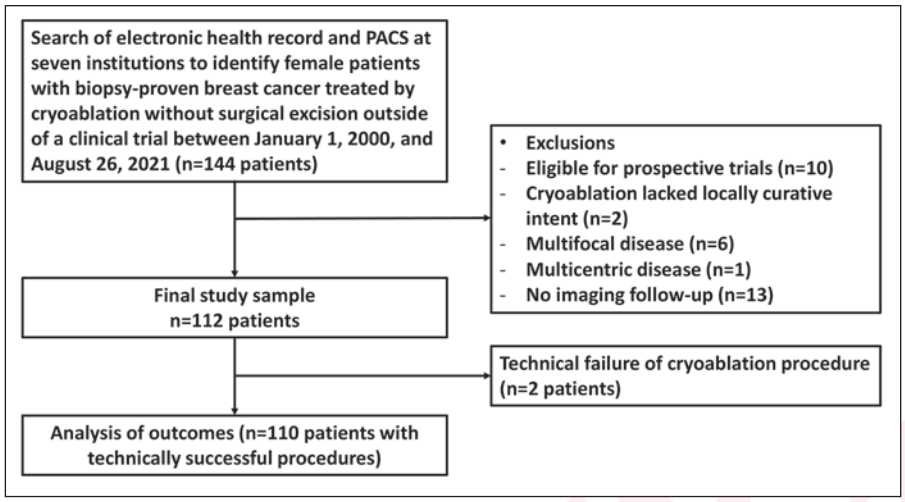

Figure 1. Flowchart of patient selection process.

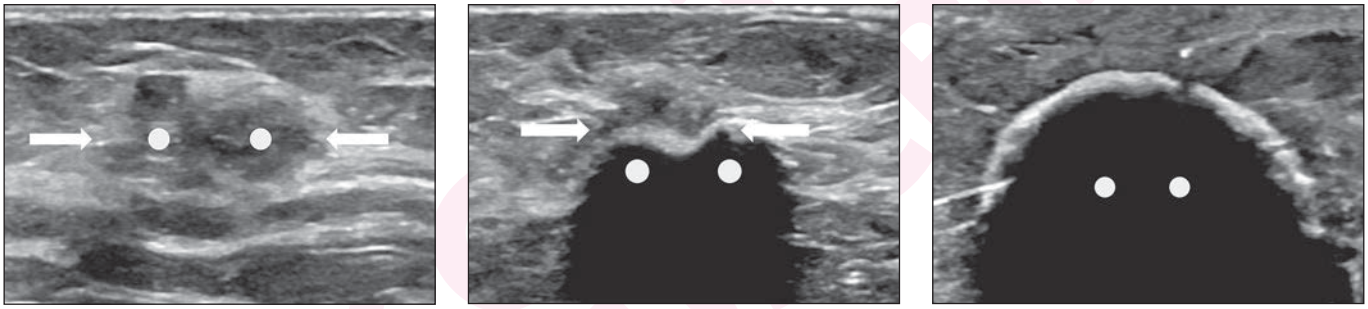

Figure 2 80-year-old woman with 1.9-cm mucinous carcinoma of the breast (Nottingham grade 1; estrogen receptor +, progesterone receptor +, HER2-), located 0.4 cm from skin. Patient elected to undergo treatment by cryoablation despite being ineligible for cryoablation clinical trials given tumor characteristics. Cryoablation was performed using argon device with transverse approach under ultrasound guidance. (A) Intraprocedural sagittal ultrasound image shows irregular hypoechoic mass in long axis (arrows). Two cryoablation needles were placed in parallel with 1.5 cm spacing to accommodate tumor size, shape, and orientation. Circles represent cryoablation needles in short axis. (B) Intraprocedural sagittal ultrasound shows two very early ice balls starting to coalesce. Ice causes anechoic posterior acoustic shadowing, which obscures cryoablation needles and begins to engulf tumor. Arrows indicate long axis of tumor. Circles represent cryoablation needles in short axis. (C) Intraprocedural sagittal ultrasound image shows that tumor is engulfed by one larger coalescent ice ball and is no longer visualized. Final ice ball size was 4.3 x 4.2 cm. Circles represent cryoablation needles in short axis.

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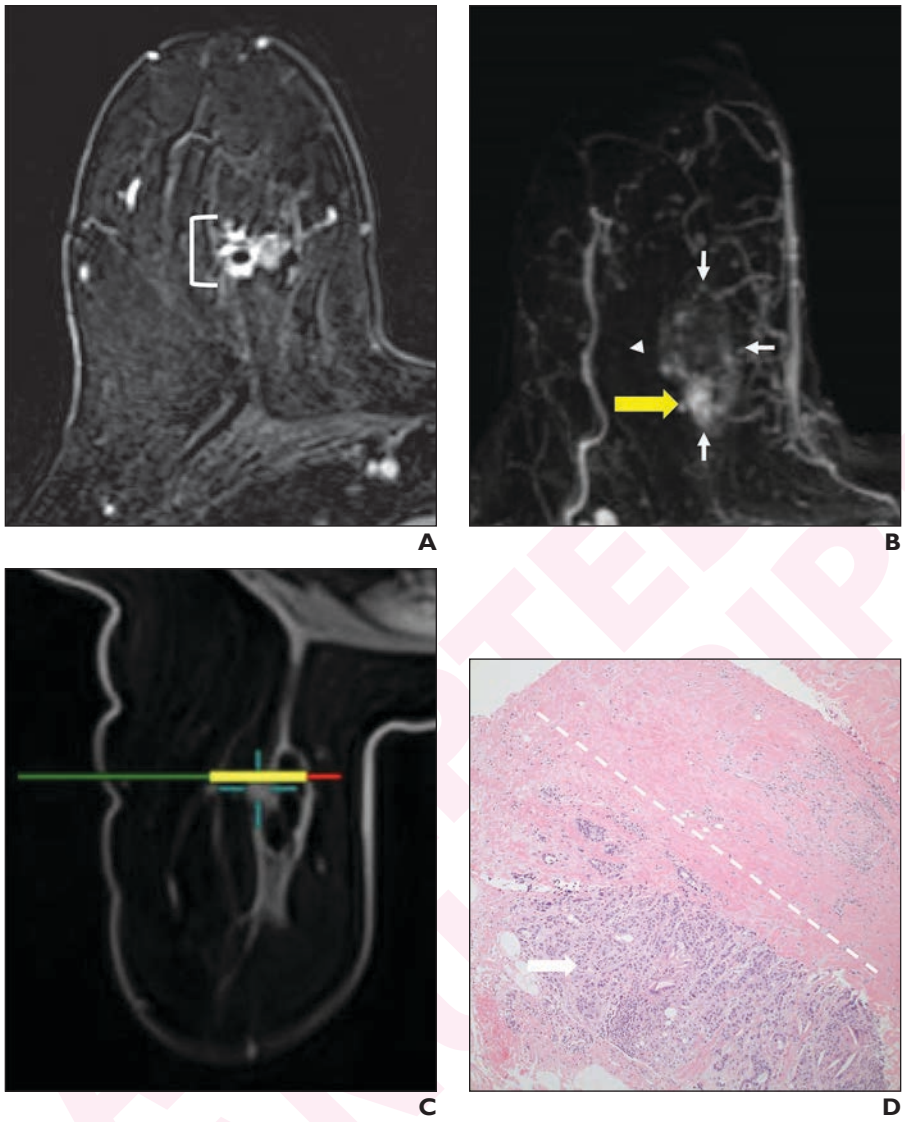

Figure 3. 73-year-old woman with right breast 1.1-cm invasive ductal carcinoma (Nottingham grade 3; estrogen receptor +, progesterone receptor +, HER2-). Patient elected to undergo treatment by cryoablation despite being ineligible for cryoablation clinical trials given tumor characteristics. (A) Axial subtracted post-contrast image from preablation MRI examination shows irregular enhancing mass (bracket), consistent with known malignancy. (B) Axial subtracted post-contrast maximum intensity projection image from 12-month postablation follow-up MRI examination shows irregular enhancing mass (yellow arrow) at ablation margin (arrowheads). Finding was considered suspicious, and MRI-guided core biopsy was recommended. (C) Image from MRI-guided biopsy procedure shows targeting of suspicious finding. (D) Photomicrograph (H&E, 20x magnification) of biopsy specimen shows post-treatment changes (top portion; demarcated by dashed line), and viable adenocarcinoma cells (bottom portion; solid arrow), consistent with ipsilateral breast tumor recurrence (IBTR). IBTR was classified as true recurrence.

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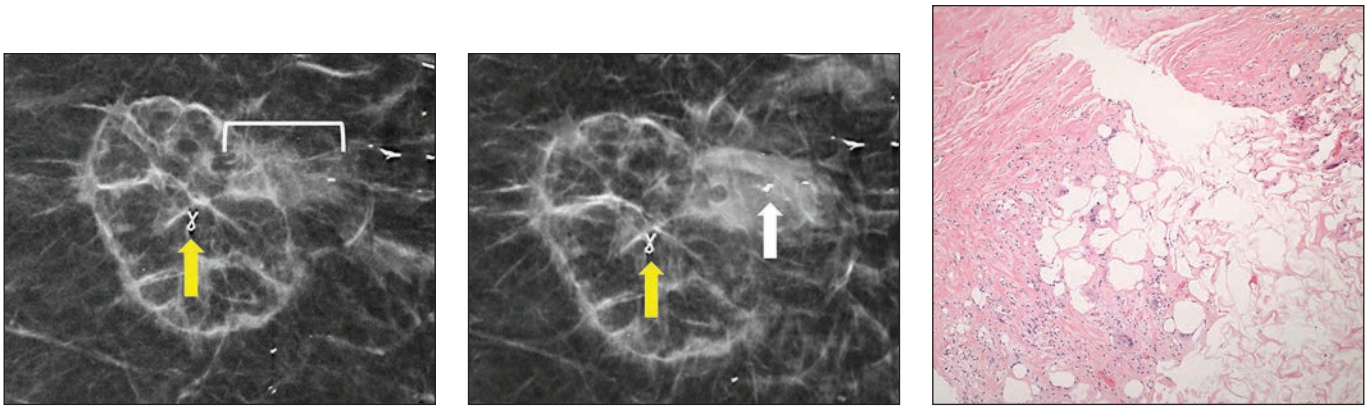

Figure 4. 91-year-old woman with 1.7-cm invasive ductal carcinoma (Nottingham grade 2, estrogen receptor +, progesterone receptor +, HER2-). Patient elected to undergo treatment by cryoablation despite being ineligible for cryoablation clinical trials given tumor characteristics. (A) Follow-up mammogram obtained 6 months postablation shows ribbon biopsy clip (yellow arrow), indicating site of treated cancer. Asymmetry (bracket) is present at anterior margin of ablation zone. Finding was considered suspicious, and stereotactic core biopsy was recommended. (B) Image from biopsy procedure shows prior ribbon clip (yellow arrow) and placement of new clip (white arrow). (C) Photomicrograph (H&E, 20x magnification) of biopsy specimen shows benign fat necrosis on background of chronic inflammation, fibrosis, and giant cells (arrowhead), without evidence of malignancy.

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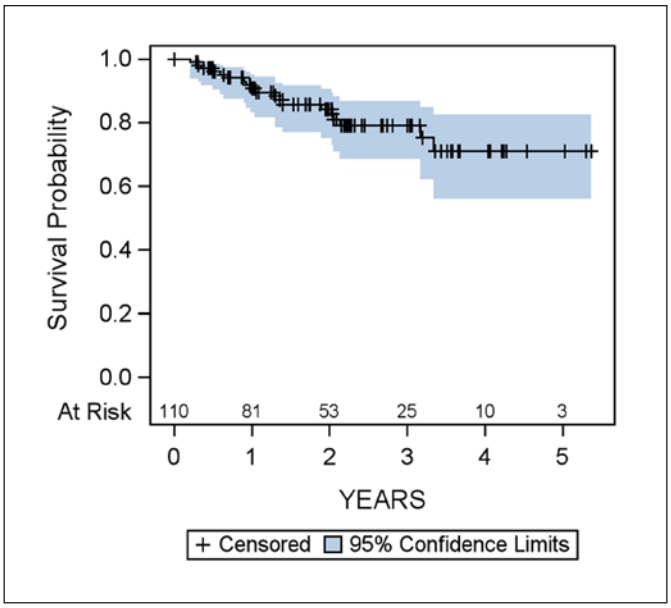

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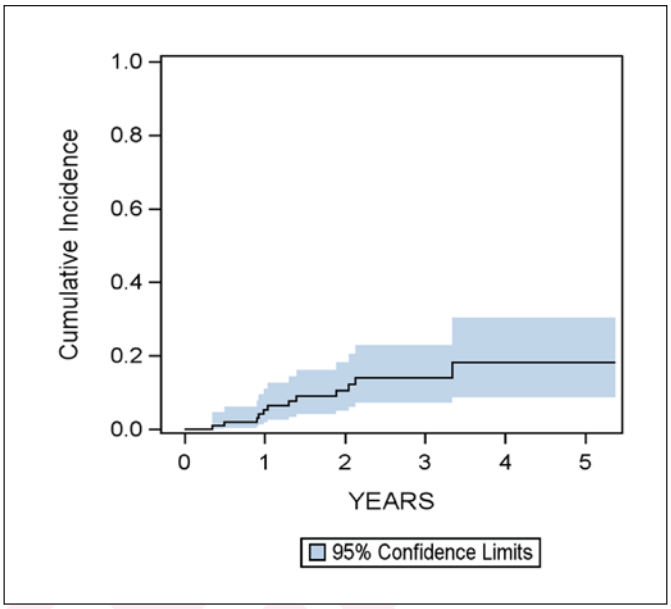

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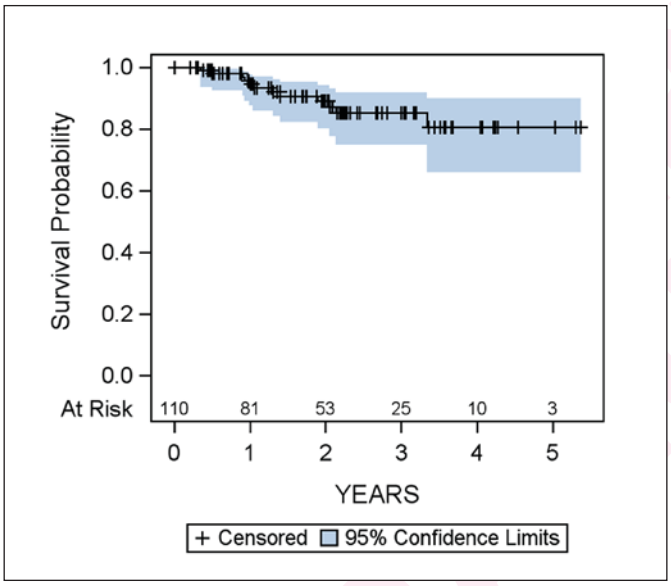

C

Figure 5. (A) Kaplan-Meier survival curve for an outcome of IBTR or death. (B) Plot of cumulative incidence of IBTR with death as competing risk. (C) Kaplan-Meier survival curve for an outcome of death. IBTR = ipsilateral breast tumor recurrence.

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Cryoablation of Primary Breast Cancer in Patients Ineligible for Clinical Trials: A Multiinstitutional Study

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There has been no financial support or source of funding for this manuscript

Disclosures
Dr Kenneth Tomkovich is a consultant and on the speaker's bureau of IceCure Medical

Manuscript type: Original research

Word count:

Data sharing statement
Data generated or analyzed during the study are available from the corresponding author by request.

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