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

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

OBJECTIVE. The purpose of this study 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 if the first follow-up imaging examination showed no evidence of residual disease. The results of follow-up biopsies were recorded. Ipsilateral breast tumor recurrences (IBTRs) 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 as a competing risk.

RESULTS. The final study sample included 112 patients (median age, 71 years). A total of seven of 112 (6.3%) patients had a minor AE; no moderate or major AEs occurred. A total of 110 of 112 cryoablation procedures (98.2%) were technically successful. During a median follow-up of 2.0 years, 22 of 110 patients (20.0%) underwent biopsy for suspicious imaging findings in the ipsilateral breast, which yielded benign concordant findings in nine of 22 patients (40.9%) and IBTR in 12 of 22 patients (54.5%). Overall, 12 of 110 patients (10.9%) experienced IBTR, including seven with true recurrence and five with new primary disease; three of 12 patients (25.0%) with IBTR had received earlier adjuvant or neoadjuvant therapy. When death was accounted for 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 and has 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 populations than those defined by clinical trial inclusion criteria.

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]. The benefits of cryoablation compared with surgery include use of local anesthesia without sedation or general anesthesia, shorter recovery times,

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improved cosmesis and patient satisfaction, and decreased cost [2, 3]. Cryoablation may be particularly beneficial for patients who are 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 [American College of Surgeons Oncology Group] Z1072 [5] and ICE3 [Cryoablation of Low Risk Small Breast Cancer] [6]) 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; patient age of at least 50 years old; 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 antigen Kiel 67 (Ki-67) proliferation index; hormone 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 should 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 shown that cryoablation is a safe and efficacious alternative to surgery for treatment of breast cancer 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. The aim of the present study 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.

Highlights

Key Finding

- *Among 112 patients excluded from clinical trials, breast cancer cryoablation had a frequency of technical success of 98.2% (110/112) and frequency of AE of 6.3% (7/112); all AEs were minor. During a median follow-up of 2.0 years, 12 of 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.*

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 EHRs at each institution were 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 were excluded for the following reasons: cryoablation lacked locally curative intent, presence of multifocal or multicentric disease (due to ambiguity in determining study outcomes in such patients), or 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 current 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, who had 1–25 years of posttraining experience. All procedures were performed using

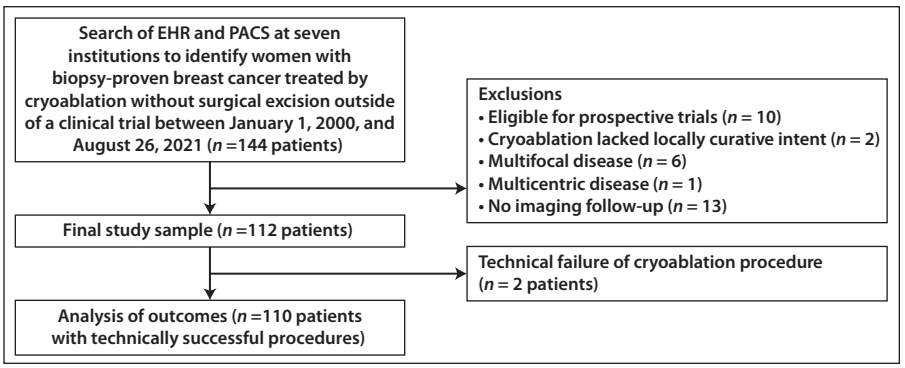

Fig. 1—Flowchart shows patient selection process.

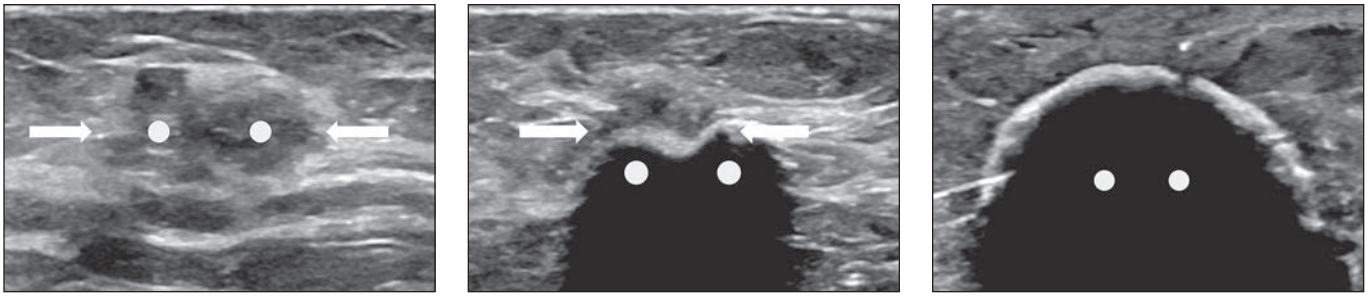

Fig. 2—80-year-old woman with 1.9-cm mucinous carcinoma of breast (Nottingham grade 1; estrogen receptor positive, progesterone receptor positive, HER2 negative) located 0.4 cm from skin. Patient elected to undergo treatment with cryoablation despite being ineligible for cryoablation clinical trials 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 image 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 × 4.2 cm. Circles represent cryoablation needles in short axis.

local anesthesia without sedation. Procedures were performed using a cryoablation device with liquid nitrogen (Visica 2 treatment system [Sanarus Technologies], ProSense cryosurgical system [IceCure Medical]) or a cryoablation device with high-pressure argon gas (Visual ICE Cryoablation System [Boston Scientific], and Cryocare SL system [Varian Medical Systems]). 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 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 on the basis of long- and short-axis measurements of both the ice and the tumor. Each procedure consisted of two freeze-thaw cycles, which typically included 5- to 10-minute freezes with an intervening 5- to 10-minute passive thaw. After 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 (AEs) and classified these events, by use of the Common Terminology Criteria for Adverse Events 5.0, as grade 1 (mild), 2 (moderate), or 3 (severe) [7].

Preablation and postablation imaging protocols varied depending on institutional availability, proceduralist preference, and patient characteristics. All patients underwent preablation imaging by mammography and ultrasound; patients may have also undergone preablation contrast-enhanced breast MRI. All patients underwent imaging follow-up after cryoablation by use of a variable combination of mammography, ultrasound, and MRI. Some institutions also used CT or FDG PET/CT as follow-up modalities. 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]. 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; the purpose for preablation imaging (screening vs diagnostic); presence of a palpable lesion; tumor laterality; performance of preablation MRI or FDG PET/CT in addition to mammography and ultrasound; the clockface location of the tumor on ultrasound (upper outer quadrant vs other location); the largest tumor dimension on ultrasound; the distance of the tumor from the nipple, skin, and pectoralis on ultrasound; the presence of a greater tumor size on MRI than on ultrasound; the maximum tumor size on MRI; the distance of the tumor from the pectoralis on MRI; and presence of nodal or distant metastatic disease [9]. MRI-related features were assessed only 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. The features of the 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 device manufactured by Boston Scientific); the number of probes used (for procedures performed using a device by Boston Scientific or Varian Medical Systems); the first freeze duration; the duration of the passive thaw; the duration of the second freeze; the total freeze duration; the maximum long- and short-axis dimensions of the ice ball; and the use and volume of intraprocedural hydrodisplacement. The types of neoadjuvant and adjuvant therapy received were recorded. Fur-

thermore, 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 for 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, if it was reported as achieving the intended treatment parameters for the targeted lesion, and if the first follow-up imaging examination was reported as showing no evidence of residual disease. Details of technical failures were recorded.

Outcomes

Outcomes analysis was performed for patients for 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 from cryoablation to the first follow-up imaging examination, the time points at which follow-up imaging was performed, and the total duration 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 determined the histologic outcomes of the biopsies.

All instances of ipsilateral breast tumor recurrence (IBTR) that were 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 terms of histology and/or location) [10]. Additional data recorded for each IBTR included the presence of a suspicious finding on follow-up imaging, the interval between cryoablation and diagnosis of IBTR, the 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. For patients who died, the time from cryoablation to death was recorded. In patients without documentation of death, the time 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 deaths.

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, for whom biopsy diagnosed IBTR. For these calculations, patients who underwent biopsy and for whom biopsy results were unavailable were classified as not having IBTR. Analysis of Kaplan-Meier curves was used to estimate the likelihood of IBTR or death during follow-up, the likelihood of IBTR when censoring for death, the cumulative incidence of IBTR when accounting for death before IBTR as a com-

TABLE 1: Patient and Tumor Characteristics at Baseline

Characteristic	Patient and/or Tumor Data (n = 112)
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)
Comorbidity	
Cardiovascular disease[a]	41 (36.6)
Lung disease[b]	13 (11.6)
Nonbreast primary cancer	11 (9.8)
Diabetes mellitus	10 (8.9)
Liver disease[c]	3 (2.7)
Dementia or mild cognitive impairment	3 (2.7)
Neurologic disorder[d]	5 (4.5)
Thyroid disorder[e]	8 (7.1)
Chronic kidney disease	4 (3.6)
At least one comorbidity	60 (53.6)
Purpose of preprocedure imaging	
Screening	88 (78.6)
Diagnostic	24 (21.4)
Palpable lesion	32 (28.6)
Laterality	
Right breast	51 (45.5)
Left breast	61 (54.5)
Preprocedure imaging[f]	
MRI	68 (60.7)
FDG PET/CT	6 (5.4)
US clockface location	
Upper outer quadrant	67 (59.8)
Other	45 (40.2)
US measurement (cm), median (IQR)	
Greatest lesion diameter	1.0 (0.7–1.8)
Distance of lesion from nipple	5.0 (3.0–7.0)
Distance of lesion from skin	0.7 (0.5–1.1)
Distance of lesion from pectoralis	0.6 (0.4–1.1)
Lesion size greater on MRI than on US[g]	17 (15.2)

(Table 1 continues on next page)

peting risk, and the likelihood of death. These outcomes were each reported at time points of 1, 2, and 3 years, along with standard errors (SEs). The IBTR models censored patients at the time of their last follow-up imaging examination in the absence of other events. The assessment of IBTR when death was accounted for as a competing risk used the method of Fine and Gray [11]; this model was confirmed to satisfy the Supremum test for proportional hazards assumption, the Schoenfeld test for 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 (G.L.B.) with 11 years of experience. Analyses were conducted using SAS software (version 9.4, SAS Institute), including the LIFETEST and PHREG procedures for outcome assessments.

TABLE 1: Patient and Tumor Characteristics at Baseline (continued)

Characteristic	Patient and/or Tumor Data (*n* = 112)
MRI measurement (cm), median (IQR)	
Greatest lesion dimension[g]	1.6 (1.3–2.3)
Distance of lesion from pectoralis[g]	1.1 (0.6–3.0)
Presence of N1 nodal and/or distant metastatic disease	5 (4.5)
N1 nodal disease	4 (3.6)
Distant metastatic disease	1 (0.9)
Histologic diagnosis	
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	32 (28.6)
DCIS percentage[h], median (IQR)	17.5 (5.0–25.0)
Nottingham grade	
1	61 (54.5)
2	40 (35.7)
3	11 (9.8)
Hormone receptor status	
ER+, PR+, and HER2–	87 (77.7)
Triple positive	4 (3.6)
ER+, PR–, and HER2–	9 (8.0)
Triple negative	10 (8.9)

Note—Except where otherwise indicated, data are count with percentage in parentheses. Percentages do not always equal 100% due to rounding. US = ultrasound, IDC = invasive ductal carcinoma, NOS = not otherwise specified, ILC = invasive lobular carcinoma, DCIS = ductal carcinoma in situ, ER = estrogen receptor, PR = progesterone receptor. Plus sign (+) denotes positive, and minus sign (–) denotes negative.
[a]Includes hypertension, heart failure, coronary artery disease, and atrial fibrillation.
[b]Includes chronic obstructive pulmonary disease and pulmonary fibrosis.
[c]Includes cirrhosis, primary sclerosing cholangitis, and primary biliary cholangitis.
[d]Other than dementia or mild cognitive impairment; includes stroke and multiple sclerosis.
[e]Includes hypothyroidism, hyperthyroidism, and thyroiditis.
[f]In addition to mammography and US.
[g]Reported only among patients who underwent MRI before ablation.
[h]Reported only among patients with a tumor with a DCIS component.

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 symptoms; seven were excluded because they had multifocal (*n* = 6) or multicentric (*n* = 1) disease; and 13 were excluded because they had no follow-up imaging performed 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 examination performed during the study interval (Fig. 1).

TABLE 2: Reasons Why Patients Were Ineligible for Cryoablation Clinical Trials

Reason	No. (%) of Patients (*n* = 112)
Age < 50 y	7 (6.3)
Greatest lesion dimension on ultrasound or MRI > 1.5 cm	40 (35.7)
Ultrasound finding	
Lesion distance from skin < 0.5 cm	27 (24.1)
Lesion distance from pectoralis < 0.3 cm	19 (17.0)
Histology other than IDC	32 (28.6)
Presence of EIC in patient with IDC[a]	9 (8.0)
Hormone receptor status not ER+, PR+, and 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)

Note—Patients were potentially ineligible for multiple reasons. IDC = invasive ductal carcinoma, EIC = extensive intraductal component, ER = estrogen receptor, PR = progesterone receptor, Ki-67 = antigen Kiel 67. Plus sign (+) denotes positive, and minus sign (–) denotes negative.
[a]Defined as ductal carcinoma in situ component of 25% or greater.

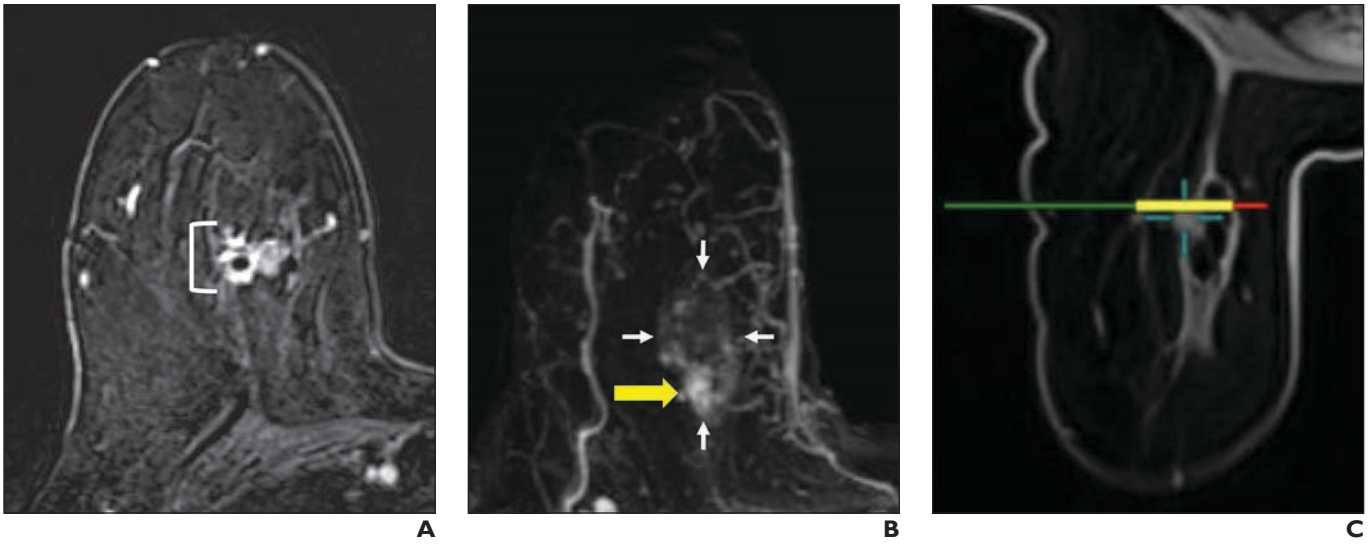

Fig. 3—73-year-old woman with 1.1-cm invasive ductal carcinoma of right breast (Nottingham grade 3; estrogen receptor positive, progesterone receptor positive, HER2 negative). Patient elected to undergo treatment with cryoablation despite being ineligible for cryoablation clinical trials given tumor characteristics.
A, Axial subtracted postcontrast image from preablation MRI examination shows irregular enhancing mass (*bracket*), consistent with known malignancy.
B, Axial subtracted postcontrast maximum-intensity-projection image obtained at follow-up MRI examination 12 months after ablation shows irregular enhancing mass (*yellow arrow*) at posterior ablation margins. White arrows denote rims of ablation zone enhancement. Finding was considered suspicious, and MRI-guided core biopsy was recommended.
C, Image from MRI-guided biopsy procedure shows targeting of suspicious finding (*caliper*). Green indicates location of cannula, yellow denotes where core copay sampling tray will be located, and red indicates headspace representing sharp point of biopsy needle.
D, Photomicrograph (H and E, ×20) of biopsy specimen shows posttreatment changes (demarcated by *dashed line*) and viable adenocarcinoma cells (*arrow*), consistent with ipsilateral breast tumor recurrence (IBTR). IBTR was classified as true recurrence.

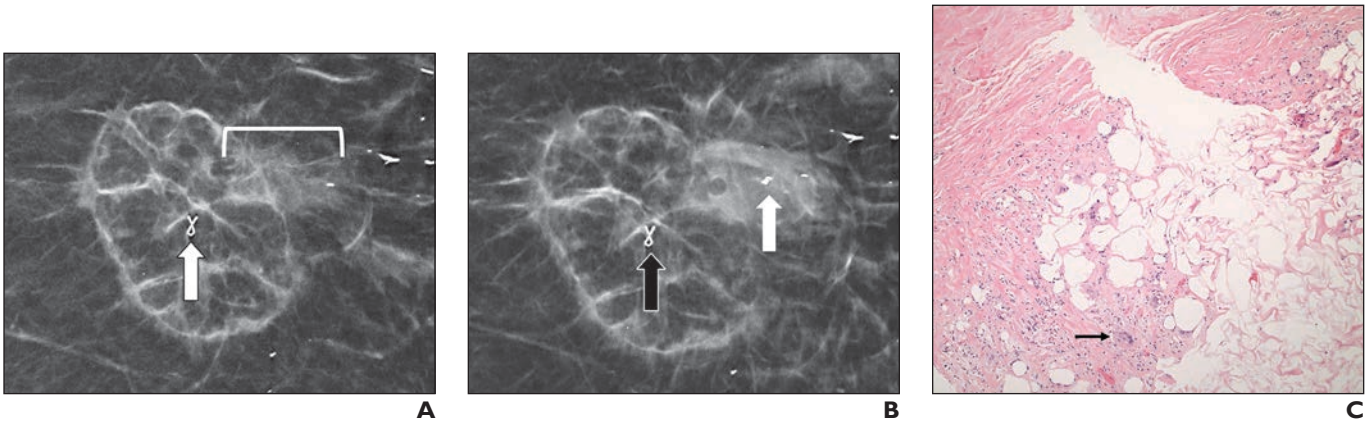

Fig. 4—91-year-old woman with 1.7-cm invasive ductal carcinoma (Nottingham grade 2; estrogen receptor positive, progesterone receptor positive, HER2 negative). Patient elected to undergo treatment with cryoablation despite being ineligible for cryoablation clinical trials given tumor characteristics.
A, Follow-up mammogram obtained 6 months after ablation shows ribbon biopsy clip (*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 (*black arrow*) and placement of new clip (*white arrow*).
C, Photomicrograph (H and E, ×20) of biopsy specimen shows benign fat necrosis on background of chronic inflammation, fibrosis, and giant cells (*arrow*) without evidence of malignancy.

Patient and Tumor Characteristics

Table 1 summarizes the baseline patient and tumor characteristics. The median patient age at the time of cryoablation was 71 years old (IQR, 62–79 years old). A total of 60 of 112 patients (53.6%) had at least one comorbidity. The median largest tumor dimension on ultrasound was 1.0 cm (IQR, 0.7–1.8 cm). On ultrasound, the median distances from the tumor to the nipple, skin, and pectoralis were 5.0 cm (IQR, 3.0–7.0 cm), 0.7 cm (IQR, 0.5–1.1 cm), and 0.6 cm (IQR, 0.4–1.1 cm), respectively. Five patients (4.5%) 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.. Of these 88 IDCs, 32 (28.6%) had a DCIS component; the DCIS percentage was reported for 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. Of the tumors 61 (54.5%) were assessed as Nottingham grade 1; 40 (35.7%), as grade 2; and 11 (9.8%), as grade 3. The hormone receptor status was ER positive, progesterone receptor (PR) positive, HER2 negative in 87 (77.7%), and triple negative in 10 (8.9%).

Table 2 summarizes the 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 of greater than 1.5 cm on ultrasound or MRI (n = 40), patient request not to undergo or inability to tolerate adjuvant therapy (n = 36), and tumor histology other than IDC (n = 32).

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

Cryoablation Procedures

Table 4 summarizes details about the 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 the Visica 2 treatment system (80/112; 71.4%). Fifteen procedures were performed using a device manufactured by Boston Scientific. This device was selected because of institutional availability (for five patients), physician preference (for four patients), small lesion size (for three patients), or the need for multiple probes for complete lesion treatment (for three patients). All procedures performed using a Boston Scientific device used at least two probes.

The median duration of the total freeze time was 14 minutes (IQR, 12–16 minutes). The median long-axis and short-axis diameters of the maximum ice ball formed during treatment were 5.0

TABLE 3: Types of Neoadjuvant and Adjuvant Therapy Received

Variable	No. (%) of Patients (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)

Note—Percentages do not always equal 100% due to rounding.

TABLE 4: Details About Cryoablation Procedures

Variable	Cryoablation Data (n = 112)
Time between biopsy and cryoablation (d)	49.5 (36–100)
Cryoablation device, no. (%) of procedures	
Liquid nitrogen	
Visica 2 (Sanarus Technologies)	80 (71.4)
ProSense (IceCure Medical)	16 (14.3)
Argon	
Cryocare SL (Varian Medical Systems)	1 (0.9)
Visual ICE (Boston Scientific)	15 (13.4)
Reason for selecting Boston Scientific cryoablation device, no. of procedures	
Institutional availability	5
Physician preference	4
Small lesion size	3
Need for multiple probes for complete lesion treatment	3
No. of probes used[a]	
1	4
2	7
3	4
4	1
First freeze duration (min)	7 (6–8)
Passive thaw duration (min)	10 (8–10)
Second freeze duration (min)	6 (6–8)
Total freeze time duration (min)	14 (12–16)
Maximum ice ball dimension (cm)	
Long axis	5.0 (4.4–5.5)
Short axis	3.6 (3.0–4.0)
Intraprocedural hydrodisplacement used, no. (%)	104 (92.9)
Intraprocedural hydrodisplacement volume[b] (mL)	50 (30–100)
Adverse events[c], no. (%) of procedures	7 (6.3)

Note—Unless otherwise indicated, data are median with IQR in parentheses.
[a]Reported only for procedures performed using a Boston Scientific or Varian Medical Systems 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, silver sulfadiazine cream, and topical antibiotics, with subsequent resolution.

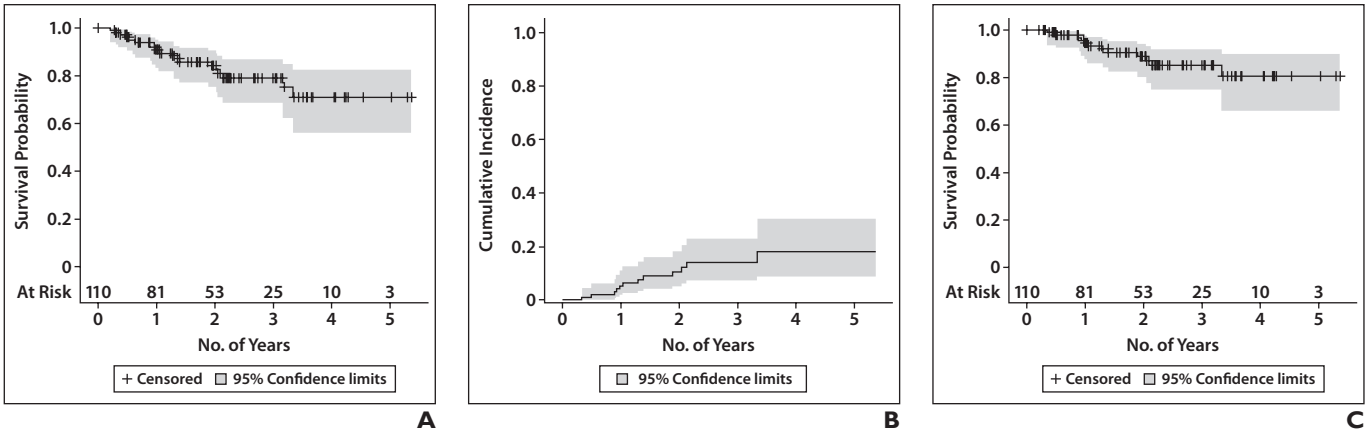

Fig. 5—Kaplan-Meier survival curves for ipsilateral breast tumor recurrence (IBTR) or death and plot of cumulative incidence of IBTR.
A, Kaplan-Meier survival curve for outcome of IBTR or death.
B, Plot of cumulative incidence of IBTR with death as competing risk.
C, Kaplan-Meier survival curve for outcome of death.

cm (IQR, 4.4–5.5 cm) and 3.6 cm (IQR, 3.0–4.0 cm), respectively. Intraprocedural hydrodisplacement was used in 104 procedures (92.9%). The hydrodisplacement volume was recorded for 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 seven of 112 procedures (6.3%) 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 had 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 had a large superficial hematoma develop 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 to prevent hypothermic skin injury. For 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 for the 110 patients for whom the cryoablation procedure was classified as a technical success. The median time from cryoablation to the first follow-up imaging examination was 76 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 for whom postablation follow-up imaging yielded expected findings, without evidence of residual or recurrent disease.

A total of 25 of 110 patients (22.7%) were recommended to undergo biopsy of suspicious findings in the ipsilateral breast on follow-up mammography (n = 12) or MRI (n = 13) performed at a median follow-up of 16 months (IQR, 6–26 months). A total of 22 of 110 patients (20.0%) underwent recommended biopsy of suspicious findings; three patients declined to undergo recommended biopsy. A total of 12 of 22 biopsies (54.5%) yielded IBTR, and nine of 22 biopsies (40.9%) yielded benign concordant findings (fat necrosis [n = 6]; fibrocystic change [n = 3]); for the remaining patient who underwent biopsy, biopsy results were unavailable. Overall, the PPV2 was 48.0% (12/25), and the PPV3 was 54.5% (12/22). The PPV2 and PPV3 were 58.3% (7/12) and 63.6% (7/11) for follow-up mammography examinations, and 38.5% (5/13) and 45.5% (5/11) 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 percentage of patients with IBTR diagnosed was 10.9% (12/110). Table 5 summarizes the characteristics and management of patients with IBTR. For these 12 patients, the median greatest dimension of the originally treated lesion on ultrasound was 1.0 cm (IQR, 0.7–1.7 cm). The hormone receptor status of the originally treated tumor was ER positive, PR positive, HER2 negative in 11 patients and ER positive, PR negative, HER2 negative in one patient. A total of seven of 12 IBTRs (58.3%) were true recurrence, and five of 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 three of 12 patients (25.0%) with IBTR, including two of seven patients (28.6%) with true recurrence and one of five patients (20.0%) 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 of 10 months (IQR, 3.8–17.5 months) after repeat cryoablation. 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 of the recurrence.

TABLE 5: Cancer Characteristics and Management for Patients With IBTR Diagnosed After Breast Cancer Cryoablation

Patient (Diagnosis)	Age at Time of Ablation (y)	Comorbidities	Greatest Dimension of Treated Lesion on Baseline US (cm)	Hormone Receptor Status of Treated Tumor	Reason(s) for Trial Ineligibility	Total Freeze Time (min)	Maximum Ice Ball Dimension (cm)		Adjuvant/ Neoadjuvant Therapy Received	Time Between Ablation and IBTR Diagnosis (mo)	Pathology of IBTR	Subsequent Management
							Long Axis	Short Axis				
1 (New primary disease)	66	Lung disease, diabetes mellitus, cirrhosis	0.8	ER+, PR+, and HER2–	Lesion < 0.3 cm from pectoralis	8	5.5	3.2	None	4	ILC, grade 2; ER+, PR+, and HER2–	Repeat cryoablation
2 (New primary disease)	63	Lung disease, cirrhosis	1.8	ER+, PR+, and HER2–	Lesion > 1.5 cm; lesion < 0.5 cm from skin; and lesion < 0.3 cm from pectoralis	16	3.5	2.9	Adjuvant endocrine therapy	6	IDC, grade 2; ER+, PR+, and HER2–	Repeat cryoablation
3 (New primary disease)	76	None	0.7	ER+, PR+, and 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+, and HER2–	Surgical excision recommended; patient lost to follow-up
4 (New primary disease)	67	None	0.6	ER+, PR+, and HER2–	Lesion < 0.5 cm from skin; lesion < 0.3 cm from pectoralis; patient declined to undergo or could not tolerate adjuvant therapy	14	3.7	2.9	None	26	DCIS, grade 3; ER+, PR+, and HER2–	Mastectomy
5 (New primary disease)	60	None	0.4	ER+, PR+, and HER2–	Patient declined to undergo or could not tolerate adjuvant therapy	12	4.9	3.6	None	12	IDC, grade 2; ER+, PR+, and HER2–	Mastectomy
6 (True recurrence)	89	CVD	1.9	ER+, PR+, and HER2–	Lesion > 1.5 cm; lesion < 0.5 cm from skin; lesion < 0.3 cm from pectoralis	12	4.5	3.6	Neoadjuvant chemo-therapy	16	IDC, grade 2; ER+, PR+, and HER2–	Standard-of-care management recommended; patient lost to follow-up
7 (True recurrence)	76	None	1.6	ER+, PR–, and HER2–	Lesion > 1.5 cm; hormone receptor status not ER+, PR+, and 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+, and HER2–	Patient declined to undergo or could not tolerate adjuvant therapy	16	4.0	3.5	None	41	IDC, grade 2; ER+, PR+, and HER2–	Repeat cryoablation
9 (True recurrence)	44	None	1.3	ER+, PR+, and HER2–	Age < 50 y; 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+, and HER2+	Mastectomy
10 (True recurrence)	77	None	2.2	ER+, PR+, and HER2–	Lesion > 1.5 cm; lesion < 0.5 cm from skin; patient declined to undergo or could not tolerate adjuvant therapy	16	5.3	4.3	None	13	DCIS, grade 3; ER+ (not evaluated for other receptors)	Mastectomy recommended; patient lost to follow-up
11 (True recurrence)	80	CVD, hypothyroidism	1.1	ER+, PR+, and HER2–	Histology other than IDC; patient could not tolerate MRI	16	6.3	5.7	Adjuvant endocrine therapy	25	IDC, grade 2; ER+, PR+, and HER2–	Surgical excision
12 (True recurrence)	51	None	0.9	ER+, PR+, and HER2–	Patient declined to undergo or could not tolerate adjuvant therapy	12	5.4	3.8	None	23	IDC, grade 2; ER+, PR+, and HER2–	Surgical excision

Note—IBTR = ipsilateral breast tumor recurrence, US = ultrasound, ER = estrogen receptor, PR = progesterone receptor, ILC = invasive lobular carcinoma, IDC = invasive ductal carcinoma, DCIS = ductal carcinoma in situ, CVD = cardiovascular disease.

A total of seven of 110 patients died during follow-up, including one patient with a cancer-related death and six patients with 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 year, 17.3% (SE = 0.04) at 2 years, and 24.8% (SE = 0.06) at 3 years (Fig. 5A). When censoring for death was done, the likelihood of IBTR was 5.4% (SE = 0.02) at 1 year, 12.8% (SE = 0.04) at 2 years, and 19.4% (SE = 0.06) at 3 years. When death was accounting for as a competing risk, the cumulative incidence of IBTR was 5.3% (SE = 0.02) at 1 year, 12.2% (SE = 0.04) at 2 years, and 18.2% (SE = 0.06) at 3 years (Fig. 5B). The likelihood of death was 3.3% (SE = 0.02) at 1 year, 6.9% (SE = 0.03) at 2 years, and 19.9% (SE = 0.09) at 3 years (Fig. 5C).

Discussion

This multiinstitutional study represents, to our knowledge, the largest study of breast cancer cryoablation among 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 being successful. 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 were 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 those defined by clinical trial criteria.

Prior single-center and multicenter 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 (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 reexcision [20].

The available literature reports variable rates of IBTR after cryoablation [5, 6, 18]. Prior prospective cryoablation studies were designed to show 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], which is lower than the frequency reported in the current study. Moreover, in the current study, when death was accounting for 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 higher frequency of IBTR in the present study. First, each patient had at least one unfavorable patient or tumor characteristic that made them 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 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 and 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 postablation 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 the present 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 current study, contrast-enhanced mammography represents an additional promising imaging modality for follow-up after cryoablation, with the potential advantages including improved PPV, reduced time and cost, increased eligibility, and increased accessibility compared with 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-fluoroestradiol PET/CT for 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 the 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 ab-

lation after a first attempted cryoablation was technically unsuccessful. Four additional patients underwent repeat cryoablation to treat recurrence and remained disease-free during the remainder of the study period (median duration, 10 months).

This study had limitations. First, it was retrospective. Second, its multiinstitutional 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. Last, the median follow-up period of 2.0 years was short.

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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(Editorial Comment starts on next page)

Editorial Comment: Breast Cryoablation—A Minimally Invasive Alternative in Breast Cancer Treatment

Breast cryoablation is an emerging minimally invasive technique with transformative potential in the development of new breast cancer therapies. This approach uses extreme cold to destroy malignant tissues. Although still in its early stages of general acceptance, cryoablation is gaining traction due to its potential to decrease the morbidity related to conventional surgical treatments for breast cancer [1]. This study by Oueidat et al. [2] evaluated the effectiveness of breast cryoablation as a locally curative treatment for patients unfit for surgery and ineligible to be enrolled in cryoablation clinical trials. The authors showed that percutaneous cryoablation can be performed with low rates of complications and local tumor recurrence in this challenging patient population.

Traditional surgery requires partial beast resection, requiring long recovery times and often causing lifelong scars and deformities, with a possible need for reconstructive surgeries. In contrast, cryoablation can be performed on an outpatient basis under ultrasound guidance and local anesthesia, allowing patients to resume their daily activities quickly [3]. This method minimizes damage to surrounding tissue, reduces complications, and improves cosmetic outcomes with high patient satisfaction and lower procedure costs.

Research into the efficacy of breast cryoablation is ongoing, but early results are promising. Complete tumor eradication after cryoablation is more likely to be achieved for tumors smaller than 1.5 cm. Traditional surgical approaches will still be necessary for larger or more aggressive tumors. Furthermore, long-term data on recurrence rates and survival outcomes are still being acquired, making it crucial for patients to thoroughly discuss the most suitable treatment options with their health care practitioners [4].

In conclusion, breast cryoablation represents a critical step forward in breast cancer treatment. Its minimally invasive approach and the encouraging outcomes from recent studies are exciting news for patients with breast cancer.

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