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ORIGINAL ARTICLE – BREAST ONCOLOGY

Cryoablation Without Excision for Low-Risk Early-Stage Breast Cancer: 3-Year Interim Analysis of Ipsilateral Breast Tumor Recurrence in the ICE3 Trial

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ABSTRACT

Background. The ICE3 trial is designed to evaluate the safety and efficacy of breast cryoablation, enabling women older than 60 years with low-risk early-stage breast cancers to benefit from a nonsurgical treatment and to avoid the associated surgical risks.

Methods. The ICE3 trial is a prospective, multi-center, single-arm, non-randomized trial including women age 60 years or older with unifocal, ultrasound-visible invasive ductal carcinoma size 1.5 cm or smaller and classified as low to intermediate grade, hormone receptor (HR)-positive, and *human epidermal growth factor receptor* 2 (HER2)-negative. Ipsilateral breast tumor recurrence (IBTR) at 5 years was the primary outcome. A 3-year interim analysis of IBTR was performed, and the IBTR probability was estimated using the Kaplan-Meier method.

Results. Full eligibility for the study was met by 194 patients, who received successful cryoablation per protocol. The mean age was 75 years (range, 55–94 years). The mean tumor length was 8.1 mm (range, 8–14.9 mm), and the mean tumor width was 7.4 mm (range, 2.8–14 mm). During a mean follow-up period of 34.83 months, the IBTR rate was 2.06% (4/194 patients). Device-related adverse events were reported as mild in 18.4% and moderate in 2.4% of the patients. No severe device-related adverse events were reported. More than 95% of the patients and 98% of the physicians reported satisfaction with the cosmetic results at the clinical follow-up evaluation.

Conclusions. Breast cryoablation presents a promising alternative to surgery while offering the benefits of a minimally invasive procedure with minimal risks. Further study within a clinical trial or registry is needed to confirm cryoablation as a viable alternative to surgical excision for appropriately selected low-risk patients.

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In 2021, an estimated 281,550 new cases of invasive breast cancer will be diagnosed among U.S. women.[1] Tumor size at diagnosis is decreasing, allowing for less aggressive surgical management. Currently, breast conservation surgery is performed increasingly for patients with early-stage breast cancer, based on long-term survival rates equivalent to those for mastectomy.[2] Moreover, significant progress in breast cancer genomics has provided a clearer understanding of tumor prognosis, allowing for a more tailored approach to patient management. We currently are able to identify those patients with more favorable tumor biology who may benefit from less aggressive surgery and adjuvant therapies.

The availability of favorable ancillary features (low grade, hormone receptor positivity) in early-stage breast cancer has led us to reconsider how we manage elderly patients. This includes avoiding radiation (CALGB C9343, Prime II) and the Choosing Wisely recommendation from the Society of Surgical Oncology, which suggests that stage 1 breast cancer patients older than 70 years who are hormone receptor (HR)-positive do not need routine assessment via sentinel lymph node biopsy.[3,4] A plausible next step would be to identify a subset of patients with early-stage breast cancer who have favorable biologic characteristics and could avoid surgical intervention altogether.

Minimally invasive ablation techniques have been explored with the intention of achieving efficacy equal to that of breast conservation therapy while avoiding the associated operative risks. Due to better understanding of tumor cryoablation at a molecular level, technological innovations of cryo-systems making extremely low temperatures stable, and precise patient selection, cryoablation currently is considered to be a safe, effective, and adaptable technique.

Cryoablation is particularly appealing because it can be performed in an office setting using local anesthesia, with better patient tolerance, improved cosmesis, and potential cost savings. This update of the ICE3 trial aims to evaluate the efficacy and safety of cryoablation without excision for low-risk early-stage breast cancer.

METHODS

Study Population

This 3-year interim analysis was a prospective, multicenter, single-arm, non-randomized trial of women age 60 years or older with unifocal invasive ductal carcinoma size 1.5 cm or smaller and with a low-risk cancer profile including estrogen receptor (ER) positivity and/or progesterone receptor (PR) positivity, human epidermal growth factor receptor 2 (HER2) negativity, and a low to intermediate histology grade (Nottingham grade $\leq$ 2) as confirmed by core needle biopsy. The patients included in the trial were clinically lymph node-negative on ultrasound and physical evaluation.

The exclusion criteria ruled out patients with an extensive intraductal component (EIC) (defined as a core biopsy specimen containing 25% or more of intraductal neoplasia), multifocal and/or multicentric disease, the presence of multifocal calcifications on mammogram, prior surgical biopsy for diagnosis or treatment of the index lesion, known coagulopathy or thrombocytopenia, patients not suitable for cryoablation according to the treating physician, and patients receiving neoadjuvant therapy in any form. Selected sites gained institutional review board (IRB) approval for enrollment of patients age 50 years or older (total of 4 patients).

The first patient was enrolled in October 2014. Initially, 211 patients were enrolled. Five patients were screen failures, and three patients were incompletely treated due to a protocol error (treatment time) recognized on chart review, in one case due to device malfunction. Consequently, 203 patients received complete cryoablation treatment and subsequent follow-up evaluation. Variation from the inclusion criteria was identified after ablation for nine additional patients, who then were excluded (5 for a tumor size $>$ 1.5 cm, 1 for EIC, 1 for multifocal disease, and 2 for previous neoadjuvant treatment before cryoablation). Thus, 194 patients met full eligibility for the study and received successful cryoablation per protocol.

Outcomes

Ipsilateral breast tumor recurrence (IBTR) at 5 years was the primary outcome. Probability of IBTR was estimated using the Kaplan-Meier method. The NCCN Distress Tool was used before the procedure at baseline and then 6 months after cryoablation.[5] The patients and physicians were required to rank their satisfaction with cosmetic results on a scale of 1 (very dissatisfied) to 5 (very satisfied) at each follow-up visit (at 6, 12, 24, 36, 48, and 60 months).

Sample Size

The primary study outcome was a local IBTR at 5 years through the width of the 95% confidence interval (CI). A sample size was calculated for this outcome. For a two-sided 95% exact Clopper Pearson confidence interval of the IBTR rate whose true value was 5%, a sample size of 150 to 200 patients was required to yield a half-width of 5% at most with more than 99% power. In this context, power is the probability (conditional method) of obtaining a

confidence interval a half-width less than or equal to the hypothesized value.

Cryoablation Technique

All the procedures were performed using the ProSense Cryosurgical System (IceCure Medical Ltd, Caesarea, Israel) (Fig. 1). This device uses liquid nitrogen to reach cooling temperatures (–196 °C). The cryoprobe achieves rapid freezing by creating an active freeze zone up to its distal tip. An isolated zone proximal to the freeze zone prevents unwanted freezing along the cryoprobe shaft. The device achieves rapid and stable cooling alternated with slow thawing that creates an ice ball with large lethal zones.

Under ultrasound guidance, the cryoprobe (140 mm/diameter 10 G) was inserted through a stab incision into the center of the lesion along the longest axis of the lesion parallel to the chest wall. Activation of the cryoablation system caused cooling of the cryoprobe to extremely low temperatures (–170 °C). This was achieved by conductive removal of heat from the tissue and consequent cell destruction by freezing.

One treatment session with a double-freezing method was used for each patient. Each freezing cycle duration was determined based on the ice ball dimension along the transverse axis (ice ball width) measured under real-time ultrasound. The freeze time stopped when the ice ball reached the predetermined ablation size. Treatment times according to the protocol were defaulted at a minimum of a 9-min freeze, 8-min passive thaw, and a second 9-min freeze.

Because the ice ball growth varies from patient to patient, treatment times were controlled at the investigator's discretion. Treatment times were adjusted to reach at least a 35-mm ice ball at the end of the first freeze and a 40-mm ice ball at the end of the second freeze, not to exceed 12 min for either freeze cycle (Fig. 1). The 35- to 40-mm ice ball size was considered necessary to create a sufficient lethal zone around the tumor with a reasonable margin based on the upper size limit of 1.5 cm for inclusion. At the end of the treatment, the probe automatically warmed to allow extraction.

The total procedure time was 20 to 40 min. The site of probe insertion was by physician preference based on lesion location, lesion orientation, or both. Successful penetration of the cryoprobe along the longest caliber of the lesion was achieved when the distance from the distal tip of the probe to the mid portion of the lesion, where the lowest temperature is expected, was approximately 20 mm.

A cautious approach was taken to avoid thermal injury to the skin and chest wall, especially for patients with small breasts. During the freezing procedure, the cryoprobe was lifted gently to prevent frost injury to the chest wall. Ultrasonography-guided injection of saline between the skin and the ice ball anterior surface was performed to avoid frost injury to the skin. All adverse event definitions and classifications were according to the Common Terminology Criteria for Adverse Events 4.0.[6]

Per protocol, adjuvant treatment was at the discretion of the treating physician. The patients were followed by clinical breast exam and breast imaging at 6 months and then annually at 12, 24, 36, 48, and 60 months after the procedure. The trial protocol was approved by the Western institutional review board (WIRB).

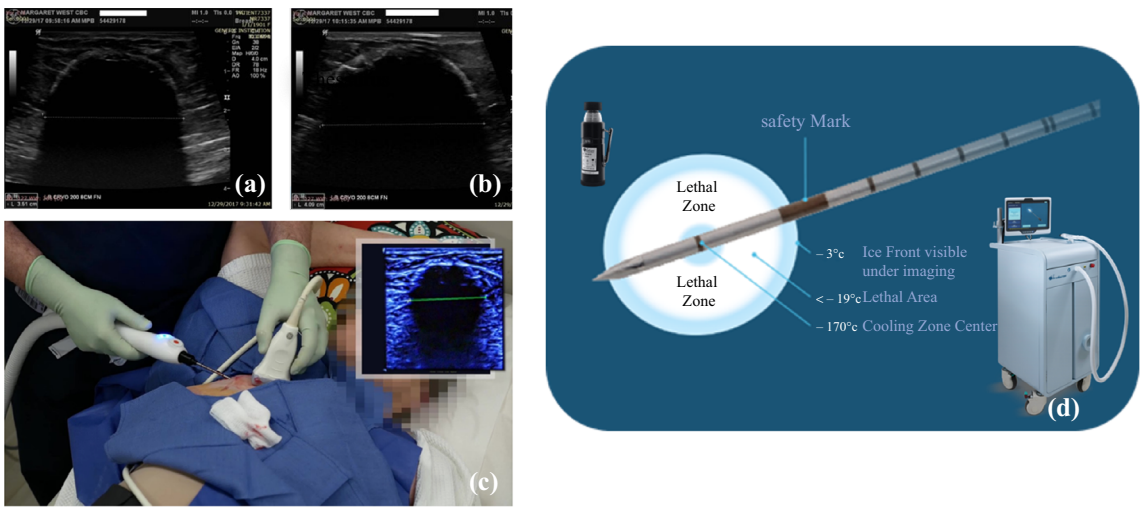


FIG. 1 IceCure crysosurgical system. **A** Ice ball after first freeze (note width of 3.5cm); **B** Ice ball after second freeze (note width of 4.0cm); **C** Hand positioning during use of the ProSenseTM Cryosurgical system (main image), real-time ice ball (top right sub-image); **D** Liquid nitrogen cannister (upper left sub-image), diagram illustrating temperatures at different points along the cryo-probe including the lethal area (main image), ProSenseTM Cryosurgical unit (lower right sub-image).

RESULTS

Characteristics and Outcomes

Full eligibility for the study was met by 194 patients, who received successful cryoablation per protocol. The mean age of the patients was 75 years (range, 55–94 years). The mean tumor length was 8.1 mm (range, 8–4.9 mm), and mean tumor width was 7.4 mm (range, 2.8–14 mm) (Table 1).

All tumors were grade 1 or 2, ER-positive, and HER2-negative, with 92.9% also showing PR positivity. After the second freeze, the mean ice ball size of the patients who did not have an IBTR during the follow-up period was 4.5 cm in the longest dimension (length) and 3.7 cm in the shortest dimension (width). At a mean follow-up period of 34.83 ± 17.96 months (range, 0.07–67.55 months), the overall IBTR rate was 2.06% (4/194 patients; 95% CI, 0.56–5.19). At the 36-month time point, the IBTR rate was 0.52% (1/194 patients; 95% CI, 0.01–2.84; Fig. 2).

The characteristics of those who met the inclusion eligibility criteria, received complete cryoablation treatment, and subsequently experienced recurrence are shown in Table 2. The mean time to recurrence was 43.1 months (range, 27.8–57.3 months). The mean tumor size was 0.7 cm (range, 0.3–1.3cm). After the second freeze, the ice ball length was 4.5 cm (range, 4.0–4.9 cm), and the ice ball width was 3.1 cm (range, 2.7–3.8 cm). Two of the four recurrences received no adjuvant treatment, and two received endocrine therapy alone.

The characteristics of those who received complete cryoablation treatment but were found to be ineligible for the analysis based on the inclusion criteria and experienced recurrence are shown in Table 3. The mean time to recurrence was 16.9 months (range, 6.1–27.7 months). The mean tumor size was 1.1 cm (range, 0.8–1.3 cm). After the second freeze, the ice ball length was 4.8 cm (range, 4.0–5.8 cm), and the ice ball width was 3.7 cm (range, 3.3–4.6 cm). Three of the five recurrences received no adjuvant treatment, and two received endocrine therapy alone. One of the two patients received the therapy for only 6 months duration.

Of the 194 patients in the study, 27 underwent adjuvant whole-breast radiation, 1 received chemotherapy, and 148 were prescribed endocrine therapy. Sentinel node biopsy was performed for 15 patients after cryoablation, 2 of whom were found to be positive. The one patient who had positive sentinel nodes received radiation and endocrine therapy. During 60 months of follow-up evaluation, this patient experienced no recurrence. The other patient had

TABLE 1 Patient characteristics of eligible cryoablated patients

Patient characteristics	
Age (years)	
Mean (range)	75 (55–94)
Median ± SD	75.7 ± 7
Race	
White	159 (82)
African American	15 (7.7)
Hispanic or Hispanic origins	12 (6.2)
Asian	1 (0.5)
Not specified/declined to answer/unknown	5 (2.6)
Tumor characteristics	
Nottingham tumor score (combine histologic grading)	
Low: 1 (range, 3–5)	98 (51)
Intermediate: 2 (range, 6–7)	96 (49)
Receptor status	
ER+	194 (100)
PR+	184 (92.9)
HER2–a	194 (100)
Tumor size by US (day of procedure)	
Mean mm (range)	Sagittal: 8.1 (8–14.9) Transverse: 7.4 (2.8–14)
Median mm ± SD	Sagittal: 8.0 ± 2.9 Transverse: 7. ± 2.7

SD standard deviation; *ER* estrogen receptor, *PR* progesterone receptor; *HER2* human epidermal growth factor receptor 2

[a]HER2 was tested with immunohistochemistry and, if equivocal, a FISH assay was performed

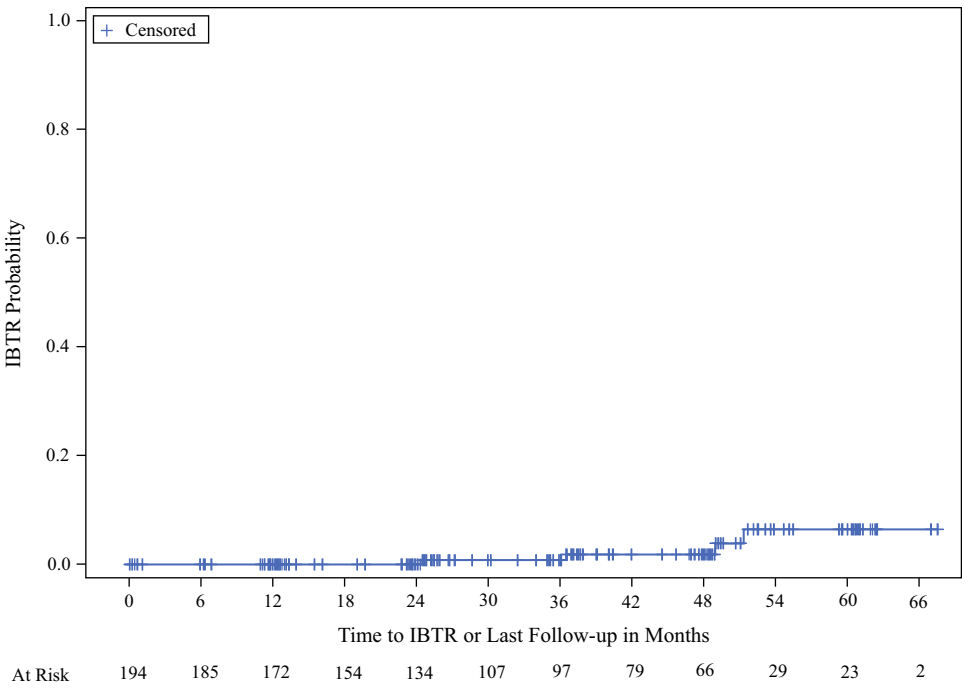


FIG. 2 Kaplan-Meier ipsilateral breast tumor recurrence (IBTR) probability curve. The overall IBTR rate was 2.06% (4/196), with an exact 95% confidence interval (CI) of 0.56–5.19%. At 36 months, the naïve IBTR rate was 0.52% (1/194), with an exact 95% CI of 0.01–2.84%. For all 194 subjects, the mean time to IBTR or last follow-up visit was 34.83 ± 17.96 months. For the 190 subjects without IBTR, the mean time to the last follow-up visit was 34.72 ± 18.06 months

TABLE 2 Characteristics of eligible cryoablated patients with local recurrence

Patient characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age	73	67	72	72
Time to recurrence (months)	57.3	51.2	27.8	36.1
Nottingham grade	2	2	2	2
Estrogen receptor	Positive	Positive	Positive	Positive
Progesterone receptor	Positive	Positive	Positive	Negative
Tumor size (cm)	0.81	1.3	0.4	0.3
Ice ball length (cm)	4.9	4.0	4.9	4.0
Ice ball width (cm)	3.8	2.9	3.0	2.7
SLNB	No	No	No	No
Adjuvant radiation (Y/N)	No	No	No	No
Adjuvant chemotherapy (Y/N)	No	No	No	No
Adjuvant endocrine therapy (Y/N)	Yes	No	No	Yes

SLNB sentinel lymphn node biopsy

chronic lymphocytic leukemia (CLL) at the cytologic assessment.

All cryoablation procedures performed were in the outpatient setting. Of the entire cohort, 76% returned to their full daily activities 48 h after the procedure. Cosmetic satisfaction was reported by 95% of the patients and by 98% of the treating physicians.

Early Withdrawal

The rate of dropout was as expected for an aging population, due to advanced age and related comorbidities. Out of 194 patients, 190 (97.9%) were disease-free at their last follow-up visit. Ten patients died of reasons unrelated to the device, the procedure, or breast cancer including heart failure, respiratory failure, nontraumatic intracerebral hemorrhage, and renal failure leading to multiorgan failure. Additionally, 18 patients were lost to follow-up evaluation due to relocation and were censored in the Kaplan-Meier analyses from their last clinical visit (Fig. 2).

Safety Evaluation

Device-related adverse events were reported as mild for 18.4% and moderate for 2.4% of the patients (Table 4). Mild adverse procedure- or device-related events included

TABLE 3 Characteristics of ineligible cryoablated patients with local recurrence

Patient characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	82	79	80	75	63
Time to recurrence (months)	12.4	27.7	6.1	23.2	15.3
Nottingham grade	2	2	2	2	2
Estrogen receptor	Positive	Positive	Positive	Positive	Positive
Progesterone receptor	Positive	Positive	Positive	Negative	Positive
Tumor size (cm)	1.3	1.0	1.3	0.8	1.0
Ice ball length (cm)	5.8	4.0	4.7	4.7	4.9
Ice ball width (cm)	4.6	3.7	3.3	3.3	3.4
SLNB	No	No	No	No	No
Adjuvant radiation (Y/N)	No	No	No	No	No
Adjuvant chemotherapy (Y/N)	No	No	No	No	No
Adjuvant endocrine therapy (Y/N)	No	No	Yes	Yes[a]	No

SLNB sentinel lymphn node biopsy

[a]6-month duration

TABLE 4 Device-related adverse events (n = 206)

no. of patients experienced AE's			23		11.2%
no. of AE's			43		20.9%
Seriousness classification					
Serious			Non-serious		
0	0%		43		20.9%
Intensity classification					
Mild		Moderate		Severe	
38	18.4%	5	2.4%	0	0%
Relation to study					
Remotely		Possible		Probable	
2	1.0%	12	5.8%	29	14.1%

bruising, localized edema, minor skin freeze burn, rash, mild bleeding from needle insertion, mild local hematoma, skin induration, mild pain in needle insertion, and pruritis. These mild adverse events were similar to those due to core biopsy. Two patients (0.9%) had moderate freeze-related skin burns, which resolved with topical treatment. No severe device-related adverse events or complications were reported.

With regard to reported adverse events, the investigator was requested to determine their relationship to the device or procedure (no or yes, and if yes, possible, probable, or remote relationship to the device) (Table 4). Two thirds of the overall adverse events were found to have no relation to the study device or procedure but rather were related to the advanced age of the subjects and their comorbidities including urinary tract infection (UTI), stroke, respiratory failure, abdominal pain, pneumonia, and headache.

DISCUSSION

Fundamentals and Biology of Cryoablation

Cryotherapy for the treatment of human disease has a long history dating back to the reported treatment of cancer by James Arnott in 1845.[7] Cryotherapy is used for various organs including lung,[8] kidney,[9] and liver,[10] among others.[11] The modern era of cryoablation began inauspiciously but had a lasting impact with the development of the closed-tip cryoprobe. Clinical experience demonstrated that precise, safe, and effective cryoablative procedures were possible.[10]

Ideal cryosurgical technique requires rapid freezing, slow thawing, and an additional freezing cycle. The destruction of the tumor relies on at least four different mechanisms: direct damage (intracellular ice formation and osmotic dehydration) and indirect damage (ischemia and immunologic response).[12–14]

Direct cellular injury occurs when freezing causes cellular dehydration. The water in the extracellular compartment freezes before the water in the intracellular compartment, which is protected by the lipid bilayer. This leads to a higher extracellular solute concentration, which causes an osmotic gradient, fluid efflux, cell shrinkage, and

distortion of the plasma membrane. It is enhanced by ice crystal formation within the cells, which further injures the integrity of organelles and the cell membrane. During the thaw, the intracellular compartment becomes hypertonic, and the resultant fluid shift causes the cell to burst.[15]

Vascular injury takes place when cryoablation causes endothelial damage to the microvasculature, which leads to platelet aggregation, vascular stasis, and micro-thrombosis. Vasoconstriction occurs in response to cooling temperatures, thereby increasing vascular stasis. This all results in ischemic death to the targeted area and furthers the coagulative necrosis.[16] Direct, cold-induced coagulative necrosis happens in the center of cryoablated lesions, whereas apoptosis has been observed at their periphery. The balance between necrosis and apoptosis has implications for the potential immunomodulation induced by cryoablation.[14,17]

The use of liquid nitrogen-based technology allows a temperature drop to − 170 °C at a very high freezing rate (> 100 °C/min) through the first minute of the freezing phase. A combination of high freezing rate with extremely low and stable temperature ensures complete cellular destruction at temperatures lower than − 19 °C.[18]

The treatment of breast diseases with cryoablation started in 1987 with benign breast lesions (fibroadenoma) and increased rapidly after 2000.[19–22] Publications on cryosurgical treatment of malignant breast cancer was proven in animal models successfully.[23] In the hours and days after cryoablation, ischemic damage occurs throughout the previously frozen area, which results in uniform necrosis. The granulation or imaged tissue shrinks over time,[19–22] leaving scar tissue and fat necrosis that reabsorbs over time (Fig. 3).

Cryoablative Success

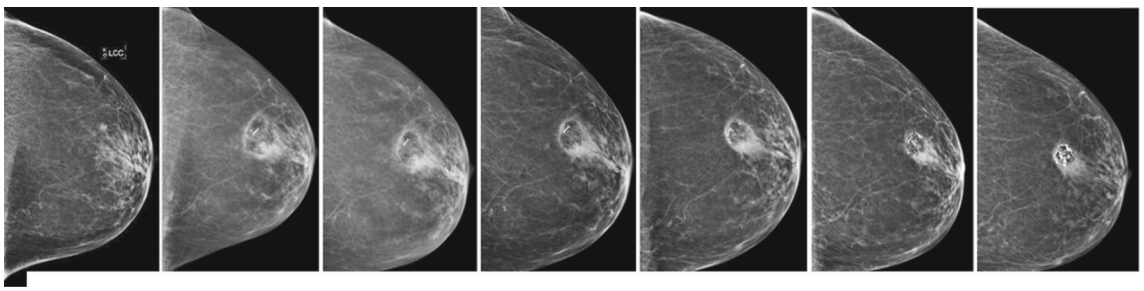
Sabel et al.[24] reported on cryoablation followed by surgical resection and pathologic assessment for tumors size 2 cm or smaller. Cryoablation was 100% (27/27) successful for all invasive ductal carcinomas size 1 cm or smaller. All patients with tumors size 1.5 cm or smaller, excluding those with invasive lobular or significant ductal carcinoma *in situ* (DCIS), also had complete ablation of all breast cancer. Cryoablation was not found to be successful for tumors larger than 1.5 cm with unselected histology.

Manenti et al.[25,26] reported two series of cryoablation for 15 and 40 post-menopausal women with breast cancers smaller than 2 cm. In the first series, the results indicated successful destruction of the target lesion in 14 of the 15 patients, with confirmation of destruction by follow-up breast magnetic resonance imaging (MRI) and pathologic assessment of the surgically excised treated area. In the second series, two patients had residual disease shown by histology that was accurately predicted by breast MRI.

In 2016, the American College of Surgeons Oncology Group (ACOSOG) completed a phase 2 study analyzing cryoablation of invasive breast cancers smaller than 2 cm.[27] Pathologic review showed successful cryoablation for 75.9% (66/87) of the patients. However, cryoablation was successful for 93.8% of the patients with tumors size 1 cm or smaller, and for 88.7% of low-grade tumors. When multifocal disease, identified at surgery, was excluded as an ablation failure, 92% (80/87) of the treated cancers and 100% of the tumors size 1 cm or smaller were successfully cryoablated.[27]

Local Recurrence

Littrup et al.[28] reported the results of a small feasibility study investigating early- and late-stage breast cancers that refused surgical treatment.[28] In their study, 11 patients with 22 breast tumors ranging in size from 0.5 to 6.5 cm were treated nonoperatively with cryoablation. The patients with early-stage breast cancer but no nodal involvement, who



(a) (b) (c) (d) (e) (f) (g)

FIG. 3 Reabsorption of fat necrosis over time with breast imaging for a 79-year-old Caucasian woman. Left breast: UOQ, 0.5 cm, hypoechoic irregular nodule, invasive ductal ca with tubular features, grade 1, estrogen receptor positivity (ER+), progesterone receptor positivity (PR+), human epidermal growth factor 2 negativity (HER2−), mammography images showing resolving zone of fat necrosis around the cryoablation treatment area **A** before cryoablation, **B** 6 months after cryoablation, **C** 12 months after cryoablation, **D** 24 months after cryoablation, **E** 36 months after cryoablation, **F** 48 months after cryoablation, and **G** 60 months after cryoablation.

refused surgical resection and were treated with cryoablation and standard adjuvant therapy, had no local recurrence during an average follow-up period of 22.8 months. For the patients with late-stage breast cancer who refused surgical intervention, cryoablation achieved satisfactory local control without evidence of local recurrence.

Adachi et al.[29] studied 193 cryoablated patients with ductal carcinoma or DCIS size 15 mm or smaller without a history of ipsilateral breast cancer or synchronous ipsilateral lesion who were estrogen receptor-positive/human epidermal growth factor 2 (HER2)-negative. The 12-month follow-up assessment showed only one (1/193, 0.5%) patient who experienced a recurrence after the treatment of invasive carcinoma. The aforementioned results are similar to those found in this study, suggesting successful cryoablation and low rates of local recurrence at the 1- to 3-year follow-up evaluation of patients with low-risk, early-stage breast cancer.

In the CALGB 9343 trial, Hughes et al.[30] randomized women age 70 years or older with hormone receptor-positive clinical T1N0 breast cancers undergoing lumpectomy to either tamoxifen with whole-breast radiation therapy or tamoxifen alone. At the 5-year follow-up evaluation, the local-regional recurrence rate for those who did not receive radiation versus those who did was respectively 4% versus 1%. At 10 years, the local regional recurrence rate had increased to 10% for those who omitted radiation versus 2% for those who received radiation. The times to distant metastasis, breast cancer-specific survival, and overall survival were similar in the two groups.[30]

Kunkler et al. studied a similar cohort of patients age 65 years or older with hormone receptor-positive tumors size 3 cm or smaller undergoing lumpectomy randomized to receive either endocrine therapy with whole-breast radiation therapy or endocrine therapy alone.[31] They found a local-regional recurrence rate for those who did not receive radiation versus those who received it to be 4.1% versus 1.3% at 5 years and 9.8% versus 0.9% at 10 years. No difference in overall survival or distant metastasis was observed.[31]

These prospective randomized trials demonstrated local-regional recurrence rates for patients receiving endocrine therapy without whole-breast radiation to be 4% at 5 years. Our 3-year interim analysis of the primary outcome suggests an IBTR on track to be similar to that in the aforementioned breast conservation trials. However, longer follow-up evaluation is necessary to determine whether these local-regional recurrence rates remain consistent between these patient cohorts.

In 2021, Habrawi et al.[32] described the results of percutaneous cryoablation used for women with diagnoses of ER+, PR+, and HER2-infiltrating ductal carcinomas size 1.5 cm or smaller. Most of the patients were older than 60 years. One cryoprobe was used per patient. All the tumors had a 1- to 2-cm freeze margin past the tumor to ensure the complete ablation of tumor tissue. None of the patients had serious complications: They all tolerated the procedure well with minimal discomfort, and no one required pain medication other than over-the-counter pain relievers. The most common post-procedure complaint was breast pain (soreness), bruising, and edema. No cosmetic deficits were reported. Of 12 patients, 11 had a 6-month follow-up evaluation at the time of publication, and 4 of the 12 patients a had 2-year follow-up evaluation. None of them had evidence of disease recurrence. As in the current study, the authors suggested that early breast cancers up to 15 mm in size with a favorable low-risk profile can be safely and effectively treated with a single session of cryoablation performed in the office without the need for subsequent surgery.

Safety and Cosmesis

Van de Voort et al.[33] recently analyzed thermal ablation as an alternative to surgical resection for small breast cancers ($\leq$2 cm). In this meta-analysis, the authors included studies evaluating various types of ablation including microwave, high-frequency ultrasound-focused, laser, radiofrequency, and cryoablation. The overall complete ablation rates for the 1266 patients studied were 86% and 85% in the cryoablation-specific cohort. The complication rates were lower among those receiving cryoablation (5%) than the rates among those receiving other types of ablation, which were as high as 18%. As with our results, cosmesis was satisfactory to excellent for the majority of the patients studied ($>$ 95%).[33]

Cryoablation performed under ultrasound guidance with local anesthesia was shown to be safe in this study. Freezing times varied (20–40 min) based on the lesion size. Minor adverse events such as bruising, minor bleeding, and pain with injection of local anesthetic were similar to those associated with core needle biopsy of the breast. Skin burns of a mild to moderate nature were treated without lasting adverse effects. In addition, cosmetic satisfaction was shown to be high ($>$ 95%) among both the patients and the treating physicians. Longer follow-up periods and additional studies will continue to establish the efficacy profile and utility of cryoablation in specific targeted populations.

Study Limitations

The results of our study are the most relevant for patients with small, low-risk, hormone-positive breast cancers and are not applicable to other populations and settings. This study also was limited by its industry-sponsored, single-arm, non-randomized nature, allowing

selection bias and potential confounders to interfere with study results.

Although patients with tumors size 1.5 cm or smaller were included in the study, the mean tumor size was only 0.8 cm. The elderly patients with biologically low-risk early-stage cancers included in our study tended to present with small tumors, especially those undergoing regular breast screening. This is especially pertinent given that patients who choose to undergo cryoablation may be more medically knowledgeable and would be more likely to participate in an annual mammography, leading to a selection bias for smaller tumor sizes at detection. Another possibility is that in starting a trial with patients whose cancers were not going to be removed, perhaps physician bias played a role in selecting for smaller tumor sizes.

The mean ice ball size in the shortest dimension (width) of the study was 3.7 cm after the second freeze, which is less than the trial protocol suggestion of 4 cm. One reason why the mean ice ball size may have been smaller than suggested by the protocol is that with laxity of the skin in elderly patients, it becomes harder to avoid freeze burn as the size of the ice ball increases. This may have caused investigators to stop freezing before 4 cm, especially if it appeared that they had a sufficient margin of ice on either side of the tumor. In light of the mean tumor size of 0.8 cm, the ice ball size required to achieve a 1-cm margin would have been 2.8 cm. Allowing variation in treatment time and size of ice ball formation among investigators is considered to be a limitation of this study.

It must be noted that this study represents a 3-year interim analysis of the primary trial outcome: the 5-year IBTR. The mean follow-up time of 34.8 months was shorter than the mean time to recurrence, which was found to be 43.1 months. Thus, the mean follow-up period in the study was not sufficient to capture many of the recurrences, which was a limitation of the study. As evidenced by the Kaplan-Meier curve in Fig. 2, IBTR is expected to increase as the follow-up evaluation continues such that we would expect more recurrences at 60 months than at 36 months. This highlights the interim nature of this study and the importance of continued follow-up assessment of these patients up to and beyond our primary 5-year end point.

The adjuvant therapies received were not standardized, which was a limitation of the study. Sentinel lymph node biopsy and other adjuvant treatments including chemotherapy, endocrine therapy, and radiation therapy were at the discretion of the treating physician and not mandated in the study protocol. Further trials investigating cryoablative therapy should standardize adjuvant therapies to minimize the confounding effects that these variations may have on study results.

CONCLUSIONS

Our 3-year interim analysis of the trial's primary outcome, IBTR at 5 years, suggests that cryoablation is safe and effective for patients with low-risk early-stage breast cancer. During the 3-year follow up period, ipsilateral breast tumor recurrence in our low-risk breast cancer cohort showed local control similar to that with surgical standard of care while avoiding the risks of a surgical procedure. Cryoablation could ultimately replace lumpectomy in this population if followed by appropriate adjuvant treatment. Subsequent analysis of ICE3 results at a 5-year follow-up assessment is necessary to validate these promising findings. Furthermore, future study within a clinical trial or registry is needed to confirm cryoablation as a viable alternative to surgical excision.

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