Original Article

Cryoablation for Treatment of Early-Stage Breast Cancer: Efficacy and Quality of Life Assessment

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Abstract

This single-center prospective study aimed to assess the safety and efficacy of cryoablation for the treatment of breast cancer (BC) subtypes 12 months post-treatment, emerging as a promising and less invasive technique. We included patients with biopsy-proven BC who underwent ultrasound-guided-cryoablation treatment during 2021-2023. Locoregional staging was performed using ultrasound and contrast-enhanced mammography (CEM). Follow-up included ultrasound at 1-, 3-, 6- and 12-months with additional CEM and biopsy at 12-months. Rate of complete ablation, tumor size and quality of life (QoL) were assessed. Primary endpoint was absence of residual tumor for BC at 12-month post cryoablation. Thirthy-six female patients (mean age, 84.5±6.7 years) with 39 biopsy-proven tumors (mean size 15.3±7.5 mm) underwent cryoablation. The 39 BCs were early-stage luminal A or B, invasive ductal carcinoma (IDC) or IDC + ductal carcinoma in situ. Complete ablation rates for BC ≤ 15 mm and BC >15 mm were 100% and 84.6%, respectively; Cryoablation positively impacted patient QoL as assessed by validated questionnaires.

Background: Breast cancer (BC) is the most common cancer among women. There has been growing interest in less invasive techniques for the treatment of breast lesions, with cryoablation emerging as promising option. We aimed to assess the safety and efficacy of cryoablation for the treatment of breast cancer tumor subtypes 12 months post-treatment. **Methods:** This single-center prospective study included patients with biopsy-proven BC who underwent ultrasound-guided-cryoablation treatment during 2021-2023. Locoregional staging was performed using ultrasound and contrast-enhanced mammography (CEM). Follow-up included ultrasound at 1-, 3-, 6- and 12-months with additional CEM and biopsy at 12-months. Rate of complete ablation, tumor size and quality of life (QoL) were assessed. Primary endpoint was absence of residual tumor for BC at 12-month post cryoablation. **Results:** Thirthy-six female patients (mean age, 84.5±6.7 years) with 39 biopsy-proven tumors (mean size 15.3±7.5 mm) underwent cryoablation. No device-related unexpected adverse events were reported. The 39 BCs were early-stage luminal A or B, invasive ductal carcinoma (IDC) or IDC + ductal carcinoma in situ. Complete ablation rates for BC ≤ 15 mm and BC >15 mm were 100% and 84.6%, respectively; Cryoablation positively impacted patient QoL as assessed by validated questionnaires. **Conclusions:** With improved QoL, cryoablation emerges as a promising, safe, and effective treatment option for low-risk breast cancer. **Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are

Abbreviations: BC, breast cancer; CEM, contrast-enhanced mammography; DCIS, ductal carcinoma in situ; FDA, food and drug administration; HER2, human epidermal growth factor receptor-2; IDC, invasive ductal carcinoma; QoL, quality of life; US, ultrasound.

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Submitted: Nov 25, 2025; Accepted: Dec 19, 2025; Epub: 22 December 2025

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https://doi.org/10.1016/j.clbc.2025.12.004

Clinical Breast Cancer, Vol. 26, No.xxx, 70–79 © 2025 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.
Keywords: Anxiety, CEM, Effectiveness, Outcomes, Local-control

Introduction

With 2,296,840 new cases globally, breast cancer (BC) was the most common cancer among women in 2024.[1,2] Currently, the standard management of early-stage BC includes mastectomy or breast-conserving surgery combined with radiotherapy. The decision to administer adjuvant systemic therapy is based on the status of lymph nodes, hormone receptors and human epidermal growth factor receptor-2 (HER2).[3] Despite the efficacy of these invasive treatment options, there has been a growing interest in less invasive techniques, aiming for noninferior curative outcomes while also recognizing the importance of maintaining or improving quality of life (QoL) and cosmetic appearance after treatment.

Some studies reported that it is a safe and effective modality and should be used as a primary alternative to surgical excision.[4,5] For over a decade, cryoablation, a minimally invasive alternative using extreme cold to destroy cells, has been successfully applied to treat fibroadenomas. In the last years the use of cryoablation was extended also to the treatment of BC, becoming a viable minimally invasive alternative to lumpectomy.[6-8] Cryoablation for breast cancer can be performed in an outpatient setting under local anesthesia with local pain control, it is associated with good patient tolerance and a low complication rate.[3] Its efficacy has been demonstrated in several studies and clinical trials in patients with early-stage, low-grade invasive ductal carcinoma hormone receptor-positive and HER2-negative BC, with a tumor size less than 15 mm.[9-11,14,15] The efficacy and safety in patients with other subtypes of low-grade BC remains to be further evaluated. Additionally, while few studies have specifically investigated cosmetic and QoL-related outcomes,[12,13,16] evaluation in diverse histological subtypes is lacking. This prospective study aimed to evaluate the safety and efficacy of cryoablation of BC and to monitor pain levels and QoL for various molecular and histological subtypes of low-grade BC at 6 and 12 months after treatment.

Materials and Methods

This study was approved by the Careggi Hospital section of the Institutional Review Board (IRB) of the Meyer Hospital, Florence, Italy (approval number 165/2024), and all patients signed an informed consent.

Study Design

This single-center prospective study investigated the safety and efficacy of liquid-nitrogen cryoablation for patients with low-grade BC tumors of various molecular and pathological subtypes treated during 2021-2023 at the Azienda Ospedaliero-Universitaria Careggi, Florence, Italy. The electronic databases were used to collect demographic, clinical and laboratory information. None of the patients underwent surgery or received radiation therapy. Patient preferences were considered for those with personal concerns about undergoing surgery (eg, lack of family support, fear of surgery/anesthesia) and for elderly patients who refused surgery. For patients deemed inoperable, various factors were taken into account, including coexisting pathologies, contraindications to general anesthesia and advanced age, leading to a palliative approach. BC patients' eligibility was limited to those ≥60 years old, with a low-grade, luminal A or B, ER-positive, HER2-negative tumor ≤35 mm, visible on ultrasound (US) without detectable lymph node involvement.

BC staging was performed with conventional imaging including US (ESAOTE, MyLab 70 XVG, Genoa, Italy) using a 10–13 MHz transducer, digital mammography and digital breast tomosynthesis, using a full-field digital mammography unit with tomosynthesis (Selenia Dimensions, Hologic, Bedford, MA, USA) and contrast-enhanced mammography (CEM) (Dimensions, Hologic, Marlborough, MA, USA) or Magnetic Resonance Imaging (MRI) for patients that were unable to undergo CEM due to kidney failure or allergy to contrast medium. MRI was performed in the prone position with dedicated breast coils (1.5-Tesla and Magnetom Avanto, Symphony, Siemens Medical System, Erlangen, Germany; Philips Medical System, DA Best, The Netherlands). All BC were confirmed by US-guided biopsy. Images were read in consensus by 2 radiologists. All BC patients were deemed inoperable by the multidisciplinary team of the Breast Unit (surgeon, radiologist, radiotherapist, oncologist) and recommended adjuvant hormonal therapy. Patients with high cardiovascular risk, severe cognitive impairment, or skin infiltration/involvement, and tumors too deep to treat were excluded. BC patients with tumors >35 mm, lymphadenopathy, triple-negative, and HER2-positive tumors were also excluded. Breast density was categorized as A (almost entirely fatty), B (scattered fibroglandular densities), C (heterogeneously dense) or D (extremely dense). Following the cryoablation procedure, patients were followed at 1-, 3-, 6-, and 12-months with US imaging and with CEM and biopsy at 1 year.

Cryoablation Procedure

Cryoablations were performed by 2 physicians with 30 and 10 years of experience in breast radiology and breast interventions, respectively. Procedures were performed with the ProSenseTM system and a 13G cryoprobe (IceCure-Medical Ltd., Caesarea, Israel) under US guidance as recommended by the manufacturer.[14] The freeze-thaw-freeze times and the ice ball size were determined based on the lesion size and location, aiming for full engulfment,

with at least 10 mm margins at each side for BC cases.[6] Subsequent surgical excision was not included in the study protocol.

Outcome Measures

Safety. Cryoablation safety was assessed by collecting adverse events (AEs) and complications reported during the procedure and at 1-, 3-, 6-, and 12-month postprocedure follow-up visits.

Efficacy. The primary outcome measure for BC was the absence of residual tumor up to 12 months postcryoablation, determined by both functional imaging (US and CEM, or MRI as specified above) and biopsy, with the biopsy result deemed conclusive. Two samples, on average, from 3 cryolesion areas (core, upper and lower peripheries) were histologically examined for residual malignancy. Secondary outcomes included cryoablation efficacy at the 12-month for specific subgroups, including Ki67 index ($\leq$ or $>$20%), tumor size ($\leq$ or $>$ 15 mm), and tumor histological features (luminal A or B, invasive ductal carcinoma (IDC) or IDC + ductal carcinoma in situ (DCIS)). Additional secondary endpoints were percentage of size reduction (US) at 12 months postcryoablation and changes in pain level, satisfaction and QoL at 6- and 12 months postcryoablation versus baseline.

Pain, Satisfaction and Quality of Life. Pain was evaluated using the Visual Analogue Scale (VAS), satisfaction and QoL were assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B)[19], Hospital Anxiety and Depression Scale (HADS) and Short Form Health Survey 36 (SF-36) questionnaires. Scores at 6- and 12-month follow-up visits were compared to baseline.

The FACT-B measures 5 domains of health-related quality of life (HRQoL), including physical, social, emotional, and functional well-being, as well as the BC subscale. Each item is assessed using a 5-point rating scale, ranging from 0 (not at all) to 4 (very much). Total scores and subscale scores for the dimension of well-being were calculated, with higher scores indicating a higher quality of life. HADS is a self-administered questionnaire for screening anxiety and depression in patients, particularly those in a hospital or medical outpatient setting, that has been validated in breast cancer patients. The scale consists of 14 items and 2 subscales (anxiety and depression), with 7 items in each. Each item is scored on a 4-point scale ranging from 0 to 3, where higher scores indicate greater levels of anxiety or depression. Total scores for each subscale were calculated by simply summing individual item responses in the subscale, ranging from 0 to 21. A score of 0-7 is considered normal, 8-10 is considered borderline abnormal (borderline case), and 11- 21 is considered abnormal (case). The SF-36 is a comprehensive, widely used survey designed to measure overall health-related quality of life. It is used in clinical practice and research to assess the impact of health conditions and treatments on a patient's life. It consists of 36 questions that cover 8 health domains, providing a broad perspective on the patient's well-being. The physical health measures include 4 scales: physical functioning, role-physical, bodily pain, and general health. The mental health measure comprises 4 scales: vitality, social functioning, role-emotional, and mental health. Each domain is scored separately on a scale from 0 to 100, where a higher score indicates better health status.

Statistics

Statistical analyses were performed using SAS 9.4 software (SAS® Institute Inc., Cary, NC.).

All patients were included in the full analysis set (FAS). The per-protocol analysis set (PPAS) includes patients who met specific criteria: BC patients with 12-month follow-up and appropriate ice ball size (mm). Appropriate ice ball size was defined as follows: [ice ball size]-[tumor size +20 mm]$\geq$0.

Results

Patient and Tumor Characteristics

Thirty-six women with 39 tumors (3 patients had bilateral tumors, 1 for each breast) who met inclusion criteria underwent cryoablation and were included in this study. BC tumor staging was performed by CEM in 28 out of the 36 BC patients (77.8%) (excluding patients with kidney failure or allergy to contrast medium) (Figure 1).

The mean age for the patients was 84.5±6.7 years (range 60-94). The mean tumor size at baseline for BC was 15.3±7.5 mm (range 5-34). The hormone receptor status of BC tumors was estrogen receptor-positive (ER+), HER2-, with 36 progesterone receptors positive (PR+), and molecular phenotypes luminal A (n=19) or B (n=20). Most BC patients (89%) had histology-proven IDC, 2 IDC + DCIS, and 2 invasive lobular carcinoma (ILC) (Table 1). Ki67 value was $\leq$20% for most BC patients (69.2%).

All patients have completed 12 months of follow-up to date.

Cryoablation Procedure

The mean procedure time was 30.4±4.2 min (range 18-37 min), with mean ice ball sizes of 36.1±6.3 mm (range 25-52 mm). One cryoprobe was typically used. For the 3 patients with bilateral tumors (one for each breast) each 1 was treated as an individual unifocal lesion.

Safety

No unexpected AEs were reported (0/39) during the cryoablation procedure and throughout the follow-up.

Cryoablation Efficacy

Among the 39 BC patients, 87.2% (34/39) (95% CI: 72.6%-95.7%) achieved complete ablation with no residual tumor at 12 months (confirmed by imaging + biopsy). A notably higher complete ablation rate of 93.8% (30/32) (95% CI: 79.2%-99.2%) was observed in PPAS analysis, excluding procedures that were not per protocol (ice ball smaller than required). The cryolesion size reduction progressively increased over the US follow-up period with a median reduction of 27.8%, 60.9%, and 100% at 1-, 3-, and 6 months post-treatment, respectively (Figure 2). Most tumors were in the upper central or outer quadrant (Figure 3A). Complete ablation rates at 12 months were further evaluated by sub-groups (Table 2). When treatment was delivered per protocol, a 100% success rate was reached for baseline tumor size $\leq$15 mm, whereas the success rate was 84.6% for tumors $>$15 mm. Both patients with mixed IDC and DCIS tumor histology exhibited residual tumor postcryoablation. Higher complete ablation rates were observed for luminal A (100%) compared to luminal B (88.9%) tumors and for Ki67

Figure 1 Study flow diagram. This diagram illustrates the study flow, detailing the total number of patients and lesions. The diagram outlines the sequence of screening, treatment (cryoablation), and follow-up evaluation.

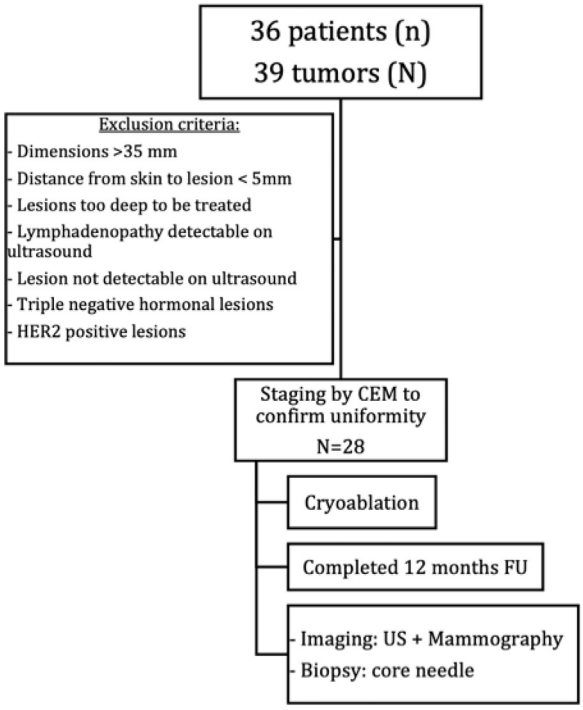


Figure 2 Tumor size reduction- BC. A box plot of the mean percentage reduction in the size of BC tumors at 12 months compared to baseline measurements. The rhombus within each box indicates the mean percentage reduction, and the circles indicate outliers.

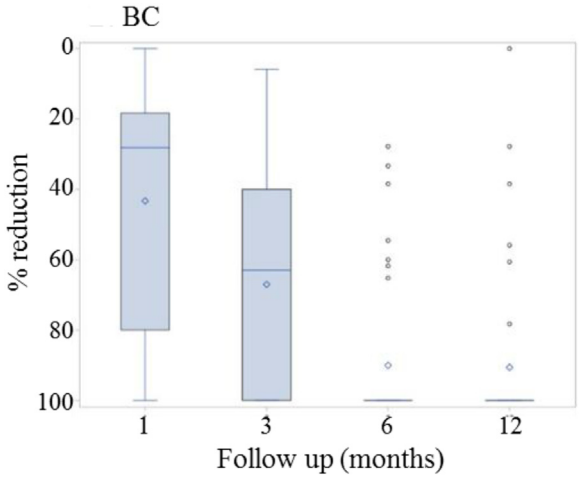


Table 1 Baseline Patients and Tumor Characteristics

		Patients
Total No. of Patients	**n**	**36**
Age (years)	Mean (SD)	84.9 (6.7)
	Median [Min, Max]	84.0 [60, 94]
Breast density		
A	n (%)	3 (6.1)
B	n (%)	14 (28.6)
C	n (%)	29 (59.2)
D	n (%)	3 (6.1)
		Tumors
Total no. of tumors	N	39
Side		
Left	N (%)	20 (51.3)
Right	N (%)	19 (48.7)
Hormone receptor status		
ER+	N (%)	39 (100.0)
PR+	N (%)	36 (62.3)
HER2-	N (%)	39 (100.0)
Ki67 ≤20%		27 (69.2)
Molecular phenotype		
Luminal A	N (%)	19 (48.7)
Luminal B	N (%)	20 (51.3)
Histology		
Colloid	N (%)	2 (5.1)
IDC	N (%)	32 (82.1)
IDC + DCIS	N (%)	2 (5.1)
IDC tubular	N (%)	1 (2.6)
ILC	N (%)	2 (5.1)
Baseline tumor size (mm)	Mean (SD)	15.3 (7.5)
	Median [Min, Max]	14 [5, 34]

Abbreviations: DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; Min = minimum; Max = maximum; SD = standard deviation; MA = not applicable; No. = number; N = number of tumors; n = number of patients.

Table 2 Complete Ablation Rates at 12 Months by Sub-Groups

Factors	**All**			**PPAS**		
	Complete Ablation	**95% CI**		**Complete Ablation**	**95% CI**	
		Low	**Up**		**Low**	**Up**
Ki67%						
>20%	83.3%	51.6%	97.9%	80%	44.4%	97.5%
≤20%	88.9%	70.8%	97.7%	100%	84.6%	100%
Baseline size (mm)						
≤15	95.5%	77.2%	100%	100%	82.4%	100%
>15	76.5%	50.1%	93.2%	84.6%	54.6%	98.1%
Luminal						
A	84.2%	60.4%	96.6%	100%	76.8%	100%
B	90.0%	68.3%	98.8%	88.9%	65.3%	98.6%
Histology						
DCIS	0.0%	0.0%	84.2%	0.0%	0.0%	97.5%
Other	91.9%	78.1%	98.3%	96.8%	83.3%	100%

Abbreviations: CI = confidence interval; DCIS = ductal carcinoma in situ; PPAS = per protocol analysis set.

Figure 3 (A) Proportion per breast quadrant. The illustration shows the distribution of tumors by type and breast quadrant. The percentage of tumors in each quadrant is indicated for BC. (B) Image findings examples for malignant tumor (BC). Image findings for malignant tumor (BC): A 78-year-old patient was diagnosed with an invasive ductal carcinoma ER+, PR+, Her2-, Ki 67 10% by tru-cut core needle biopsy. The patient was not eligible for surgery due to high cardiovascular risk. Baseline images, per-cryoablation, were performed with standard mammography (B1), US (B2) and CEM (B3), all showing a tumor in the central quadrants of the left breast. Standard mammography showing an irregular opacity, visible both in CC and MLO (white arrows) (B1). US showing a hypoechoic nodule (1.08 × 1.27 cm), corresponding to the malignant lesion undergone tru-cut core needle biopsy (B2). CEM staging, demonstrating an irregular mass with high conspicuity visible in CC and MLO, corresponding to the opacity seen in low-energy images and to the biopsy-proven malignant index tumor (white arrows) (B3). US images during cryoablation procedure showing the ice ball engulfing the lesion with appropriate margins (10 mm) of the nodule (B4). US follow-up imaging 3 months postcryoablation showing a hyperechoic halo surrounding a hypoechoic area (0.8 cm) corresponding to residual effects of cryoablation procedure (B5). US follow-up imaging 6 months postcryoablation showing no visible hypoechoic area (B6). US follow-up imaging 9 months postcryoablation showing a small hypoechoic mass corresponding to fat necrosis/phlogosis proven by tru-cut core needle biopsy (confirmed as a benign lesion) (B7). CEM follow-up imaging 12 months postcryoablation showing no visible enhancement in CC and MLO (B8). CC = craniocaudal; CEM = contrast-enhanced mammography; LMLO = left mediolateral oblique; LCC = left craniocaudal; MLO = mediolateral oblique; RMLO = right mediolateral oblique; RCC = Right craniocaudal; US = ultrasound. '+' signs mark lesion dimensions.

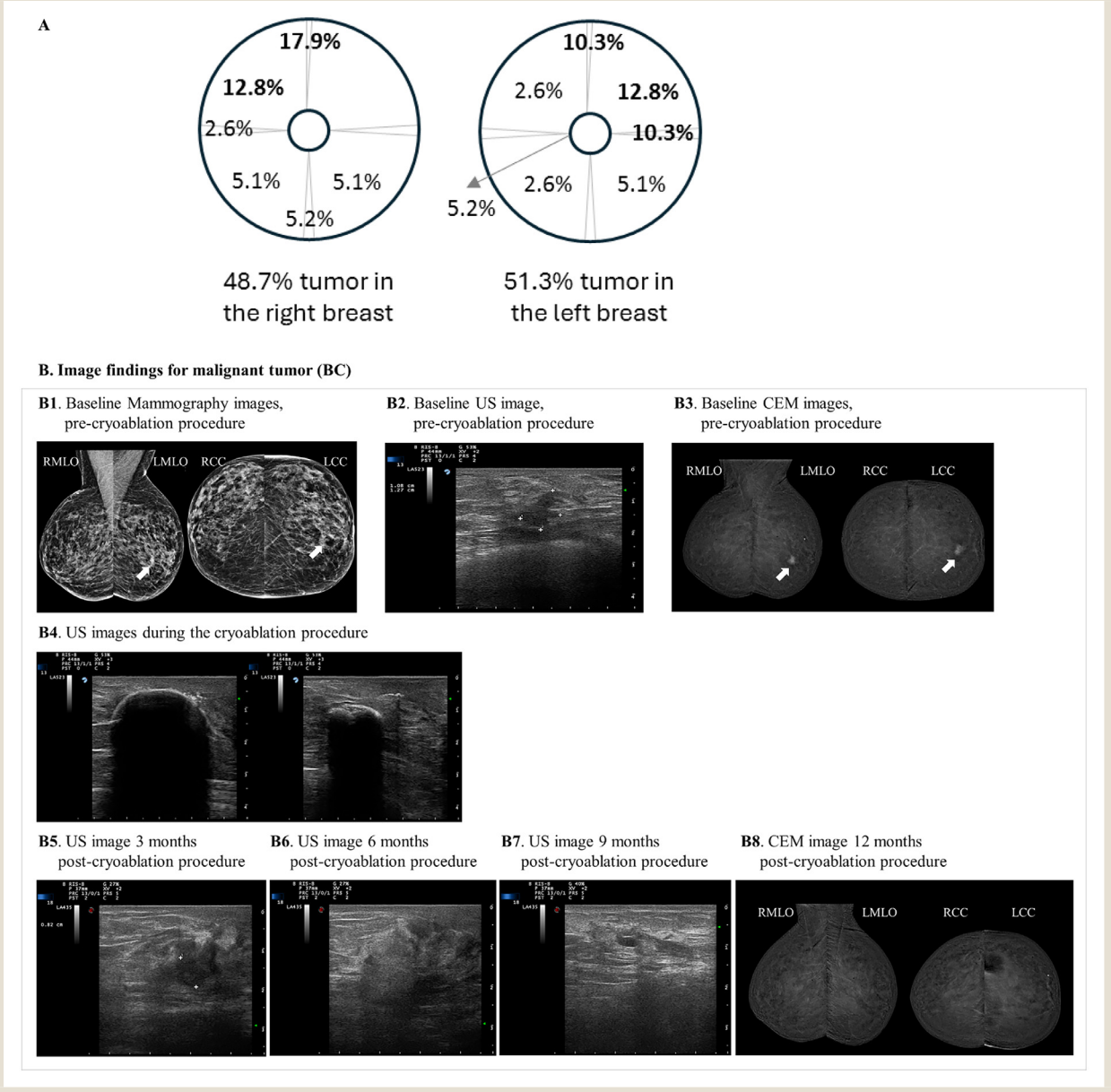
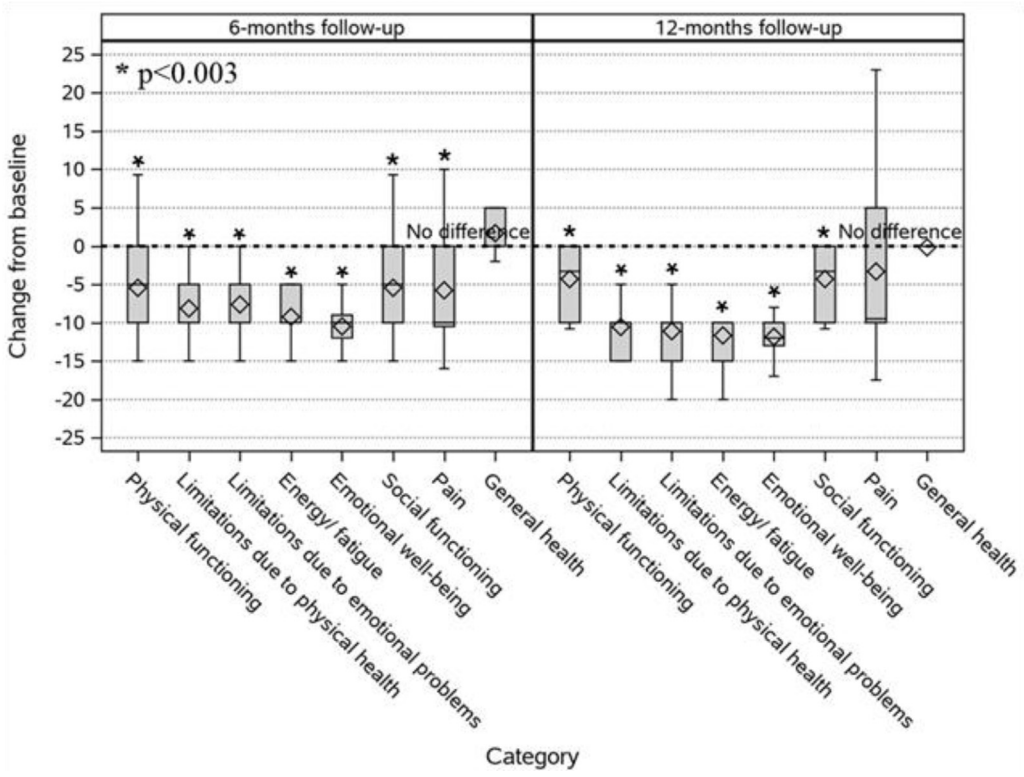


Figure 4 SF-36 questionnaire- change from baseline. A box plot of the mean change from baseline in the 8 health domains in the SF-36 questionnaire at 6 and 12 months for patients with BC. The rhombus within each box marks the mean percentage reduction. '*' denotes statistical significance ($P < .003$).



≤20% (100%) compared to Ki67 >20% (80.0%). Yet, none of the differences were statistically significant. Overall, although differences weren't statistically significant, patients with Ki67 ≤20%, luminal A, non-DCIS, or tumors ≤15 mm had the best outcomes, achieving 100% complete ablation at 12 months.

An example for image findings at baseline (standard mammography, US and CEM, Figure 3B, B1-3), procedure (US, Figure 3B, B4), and 3-, 6-, 9-, and 12 month FU (US, or CEM, Figure 3B, B5-8) for a 78-year-old patient diagnosed with an invasive ductal carcinoma ER+, PR+, Her2-, Ki 67 10%, are shown in Figure 3B. The lesion, 1.08 × 1.27 cm at baseline, which was completely engulfed by the ice ball (including 10 mm margins), was reduced in size at 3-, 6-, 9-, and 12-months post cryoablation with no residual malignancy as demonstrated by tru-cut core needle biopsy and CEM.

Quality of Life

(1) Pain assessment (VAS)
A statistically significant reduction in VAS score, with a median decrease of 1 unit, was reported 6 months postcryoablation and remained consistent at 12 months (p=.0087 and p=.0028, respectively).

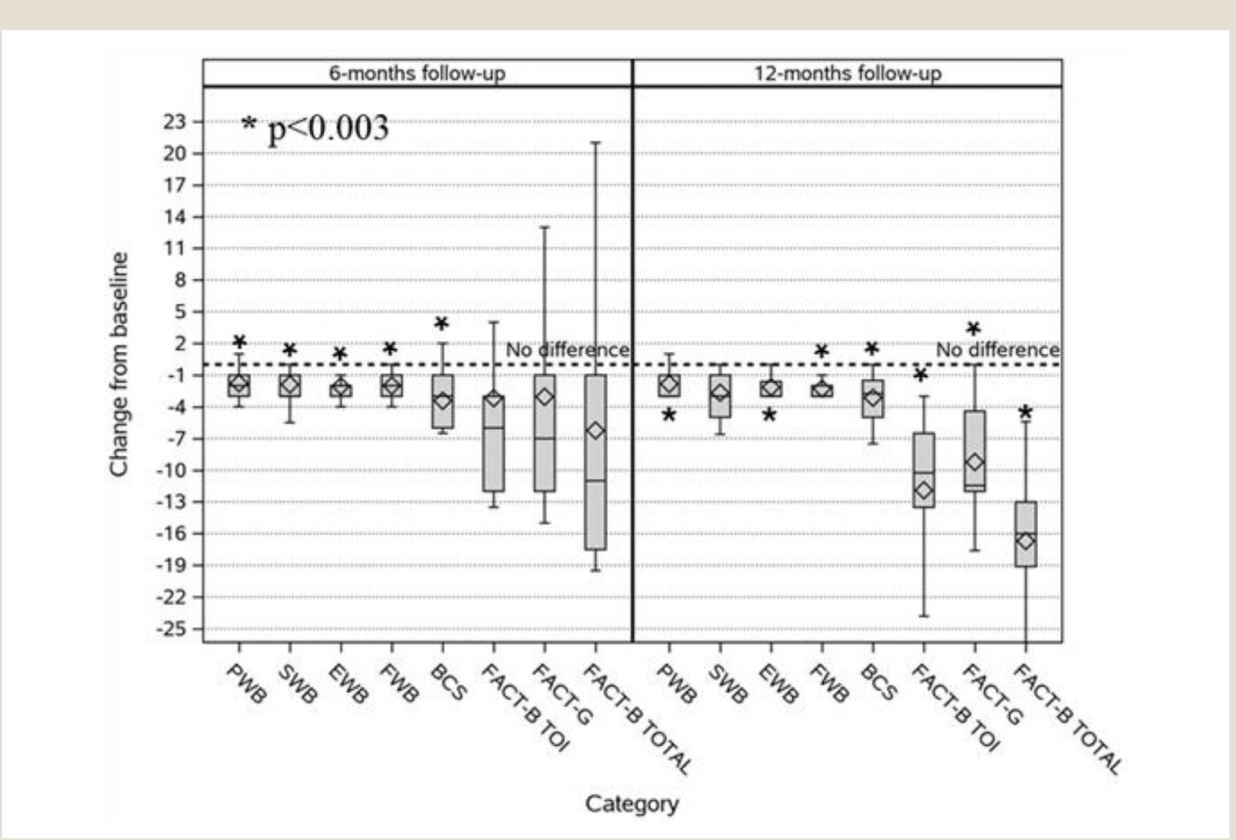
(2) FACT-B, HADS and SF-36 questionnaires

At 6 months, statistically significant improvements in all the SF-36 subscales, aside from general health, were recorded ($P < .003$) (Figure 4, Tables S1, S2 and S7). Similarly, all FACT-B factor scores were significantly higher at 12 months FU compared to baseline ($P < .003$) (Figure 5, Tables S3, S4 and S7), with the largest improvement observed for SWB and BCS. The HADS questionnaire showed that both depression and anxiety significantly improved ($P < .0001$) at 6- and 12-months FU compared to baseline, from a mean of 6.8 and 7.6 (borderline) to 5.3 and 6.1 (normal), respectively (Tables S5, S6 and S7).

Discussion

Cryoablation treatment of breast cancer is emerging as a viable minimally invasive alternative to standard surgery.[17,18] While the efficacy, safety, cosmetic and QoL outcomes of cryoablation have been demonstrated for other specific tumor types, data is limited for early-stage BC.[22-24] Consequently, this study aimed to assess the safety, efficacy, and QoL of cryoablation using the ProSenseTM System for patients with various molecular and histological subtypes of low-grade BC at up to 12 months FU. The results of this study indicate that cryoablation for patients with various molecular and histological subtypes of low-grade BC is both safe and effective,

Figure 5 FACT-B questionnaire- change from baseline. A box plot of the mean change from baseline in each of the 5 domains of health-related quality of life (HRQoL) in the FACT-B questionnaire at 6 and 12 months for the BC patients. PWB, Physical Well-Being; SWB, Social/Family Well-Being; EWB, Emotional Well-Being; FWB, Functional Well-Being; BCS, Breast Cancer Subscale; FACT-B, Functional Assessment of Cancer Therapy – Breast; FACT-G, Functional Assessment of Cancer Therapy - General; TOI, Trial Outcome Index. FACT-B TOI is the combination of PWB + FWB + BCS scores. FACT-G is the combination of PWB + FWB + BCS + FWB scores. FACT-B TOTAL combines PWB + SWB + EWB + FWB + BCS scores. The rhombus within each box marks the mean percentage reduction. '*' denotes statistically significant ($P < .003$).



achieving 100% complete ablation for BC ≤1.5 cm and 93.8% for BC ≤3.5 cm, at 12-month FU, positively impacting patients' QoL.

The cryoablation procedure was well-tolerated, without significant complications, consistent with previous studies.[16,17] In a meta-analysis of 37 studies on thermal ablation for small BC (≤2 cm), Van de Voort et al.[17] reported a 5% complication rate (14/283 patients), with cryoablation showing the lowest complication rate among other ablative techniques and much lower compared to lumpectomy alone.[18]

Breast tumor location plays a critical role in cryoablation success and safety, requiring a safe distance from structures like the nipple, skin surface (5-10 mm), and pectoralis or chest wall (3 mm), to prevent burns, the most common complications during cryoablation.[19,20] Techniques like hydrodissection, which distances the ice ball from critical structures, help shield critical areas. In addition, breast tissue composition across quadrants influences cryoprobe positioning, particularly in denser breast quadrants.[21] This study safely managed tumors across all breast locations and tissue densities, reinforcing the treatment's overall safety across diverse tumors.

Cryoablation improved QoL scores in all 3 questionnaire factors, including reduced depression and anxiety with the largest improvement in the PWB score.

Cryoablation has been most commonly applied to BC patients with tumor size ≤2 cm, unifocal tumors, ductal (rather than lobular) histology, low intraductal component, HR+, HER2-negative, ≥10 mm from the skin surface. The ICE3 trial (NCT02200705) investigated the safety and efficacy of BC cryoablation without excision in women ≥60 years with early-stage IDC, ≤1.5 cm, HR+ and HER2- concluded that cryoablation is a safe and effective treatment with a local recurrence rate of 2.06% in 3 years[10] and 4.3% at 5 years, similar to surgical procedures.[11] The Z1072 phase II trial reported a 92% success rate for lesions <20 mm and a 100% success rate for <10 mm.[9] The current study echoed those results but with larger tumors and variable histological subtypes.

Insufficient ice ball margins in 3/5 patients with residual tumors highlight the importance of precise cryoprobe placement and margins of at least 10 mm.[17] Mixed histology (IDC and DCIS)

in 2/5 patients complicates complete ablation due to the difficulty to visualize DCIS-associated microcalcifications with US.[7] Consequently, patients with this subtype are often excluded from cryoablation clinical trials for BC. However, currently, trials are ongoing investigating cryoablation's potential to prevent DCIS progression to invasive BC (NCT05218044). Nevertheless, 1 key advantage of cryoablation is that it allows for repeat procedures in cases of incomplete ablation.

Three of the 5 patients with residual malignancy had tumor sizes ≥30 mm (in addition to having mixed tumor histology of IDC and/or DCIS or insufficient ice coverage), suggesting that both histology and tumor size played a role in the incomplete ablation. This highlights the need to consider patient profiles and procedural details when performing cryoablation correctly.

This study, consistent with the ICE-3 trial and other published experiences, explores cryoablation as a potentially resolutive treatment for selected breast cancer (BC) patients, aiming to de-escalate traditional therapies. The primary goal is to minimize toxicity and reduce the overall treatment burden by avoiding additional aggressive interventions like surgery, radiotherapy, or chemotherapy after cryoablation.

While radiotherapy is generally recommended following breast-conserving surgery, it can be omitted in specific scenarios.[27-29] These include extremely small, low-risk tumors identified through molecular profiling (eg, low-risk luminal A), advanced cardiopulmonary disease, prior radiation to the same area, or patient preference after informed consent. In addition, there is increasing trend to avoid radiotherapy in elderly patients.[30,33] Hence, considerations such as radiation treatment duration, potential impact on quality of life, and the need for a caregiver as support throughout the entire duration of the therapy are crucial in tailoring treatment.[24,25]

Adjuvant hormonal therapy, a cornerstone for treatment of hormone receptor-positive BC, was recommended for all cryoablation patients in our institution, despite potential side effects.[27] However, it may be withheld in extremely low-risk tumors, particularly in elderly patients with poor prognosis, or when contraindicated by conditions like extensive thromboembolic risk (tamoxifen) or osteoporosis (aromatase inhibitors).[31,32]

Similarly, chemotherapy is often avoided when genomic analysis (eg, low Oncotype DX score) indicates minimal recurrence risk. It is also contraindicated in frail patients or those with end-stage comorbidities like severe renal or cardiac insufficiency, where risks outweigh benefits. In these cases, particularly when hormonal therapy or chemotherapy are the only alternatives, cryoablation becomes a vital treatment option for patients unfit for surgery. This approach allows for combination with palliative interventions, offering a personalized, less invasive strategy.[22,25]

Furthermore, effects of cryoablation on the immune system have been described. Therefore, to explore the potential synergies between cryoablation and systemic therapies is an open and highly relevant field of research that requires further study. Immunotherapy, with its recent successes in treating solid tumors, underscores the urgency of keep on investigating.[26]

BC patients treated with cryoablation also showed notable improvements in the degree of satisfaction as well as in health-related QoL, as measured by 3 disease-specific questionnaires. QoL has become an increasingly important issue to be considered in BC treatment decisions. Studies suggest that cryoablation provides a better overall patient experience, along with improved psychosocial and physical outcomes[13] compared to more invasive procedures such as lumpectomy.[12] Although this study did not directly compare QoL results with those of breast-conserving surgery patients, our findings support the role of cryoablation as an effective minimally invasive alternative for early-stage BC treatment.

Overall, cryoablation, while not universally applicable, represents a valuable therapeutic alternative for BC patients with specific criteria, such as small, low-risk tumors or severe comorbidities. It offers a noninvasive, less toxic option compared to traditional treatments.[22,31] Further research is essential to refine patient selection and optimize cryoablation's role in breast cancer management.[32,33]

Limitations of this study include its nonrandomized, single-center design, which may result in selection bias and residual confounding. Additionally, the lack of socio-economic data collection may have limited a more refined analysis of health-related QoL post-treatment. Lastly, the follow-up period was relatively short; however, patients continue to be monitored to gather long-term outcomes. A larger number of patients is needed to validate these findings further. Notwithstanding these drawbacks, the current study represents one of the largest experience from e single institution, recruited in a limited time span (2021-2023).

Conclusions

Cryoablation has proven to be a safe and effective treatment for early-stage BC, regardless of lesion size (up to 34 mm) or subtype (luminal A or B), showing a positive impact on patient QoL. While further randomized trials and long-term studies are necessary, the outcomes of this study contribute to the growing evidence that supports cryoablation as a valuable and effective treatment option for early BC, especially in elderly patients with comorbidities.

Clinical Practice Points

- Cryoablation is a minimally invasive treatment emerging as a valuable option for women with early-stage tumors not eligible for surgery.
- Contrast-enhanced mammography (CEM) is a useful tool to assess treatment accuracy by comparing pretreatment staging with postcryoablation response, showing precise concordance between enhancement and histological findings.
- Cryoablation is safe, effective, and well tolerated by patients.
- Patients report excellent outcomes, including reduced anxiety and improved quality of life compared with conventional surgery.
- The procedure allows rapid recovery, better cosmetic results, and represents a clinically viable alternative for nonsurgical candidates.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Careggi Hospital section of the Institutional Review Board of Meyer Hospital (approval number 165/2024).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors on request.

Disclosure

The authors have stated that they have no conflicts of interest.

CRediT authorship contribution statement

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Acknowledgments

This research received no external funding.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clbc.2025.12.004.

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