Cryoablation versus Breast Surgery in the Local Treatment of Early-Stage Breast Cancer: Protocol for the CRYSTAL–SIX Trial (CRYoablation for Small Tumors As Local Treatment)

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Background

Breast-conserving surgery followed by radiotherapy remains the standard of care for early-stage breast cancer. However, interest in minimally invasive alternatives has grown[1]. Cryoablation is a nonsurgical, image-guided technique that induces tumor cell death through freezing and thawing, avoiding general anesthesia and hospitalization[2,3].

The CRYSTAL–SIX trial (CRYoablation for Small Tumors As Local treatment – SIX) is a phase III study evaluating whether cryoablation is non-inferior to standard breast surgery in terms of locoregional control and cost-effectiveness.

Two landmark trials have shaped modern de-escalated care:

- **SOUND trial** showed that omitting axillary surgery in tumors ≤2 cm with negative axillary ultrasound was non-inferior to sentinel lymph node biopsy.
- **FAST-Forward trial** demonstrated that 26 Gy in five fractions over one week was non-inferior to 40 Gy in 15 fractions over three weeks for local control and normal tissue effects over five years.

These findings, combined with the advantages of cryoablation, led to the SIX trial design, which integrates cryoablation, omission of axillary surgery, and ultrahypofractionated radiotherapy—completing treatment in just six days.

Methods and Materials

This phase III, randomized, controlled, multicenter trial compares cryoablation to breast surgery in 750 patients with unifocal, invasive breast carcinoma (≤2.0 cm, T1N0M0), visible on ultrasound and eligible for upfront surgery.

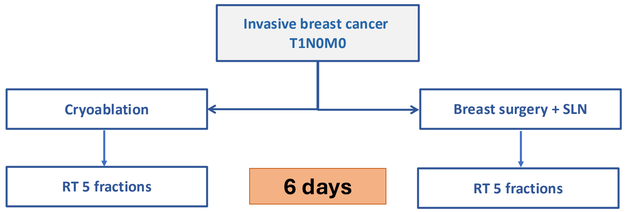
Cryoablation will be performed using Cryocare® or ProSense IceCure® under local anesthesia and ultrasound guidance.
- Surgery includes lumpectomy or mastectomy with sentinel lymph node biopsy. Axillary surgery is omitted in the cryoablation arm. All patients will receive adjuvant treatment according to tumor biology. When indicated, radiotherapy will be delivered as 26 Gy in five fractions over one week.

The study incorporates a de-escalated strategy by omitting axillary surgery, applying ultrahypofractionated radiotherapy, and using liquid biopsy for monitoring. Approved by the Ethics Committee, recruitment began in March 2025 and ends in 2030.

Registered at ClinicalTrials.gov (NCT06839001).

CRYoablation for Small Tumors As Local Treatment – SIX Trial (CRYSTAL – SIX)

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SIX Trial



Primary outcomes
1. Locoregional recurrence in 5 years
2. Cost-minimization in 1 year

Secondary outcomes
1. Locoregional recurrence in 1 year
2. Disease-free survival in 5 years e Overall survival in 5 years
3. Circulating Tumor Cells 0/6 e 12 m
4. Patient satisfaction (Breast-Q questionnaire) in 1 month
5. Quality of life (EQ-5D questionnaire) in 1 year

Chart 1. Study design

Objectives

Primary:
- Demonstrate non-inferiority of cryoablation vs. surgery for local treatment over five years
- Compare direct treatment costs over one year

Secondary:
- Locoregional recurrence at one year
- Disease-free and overall survival at five years
- CTCs at one year
- Patient satisfaction will be measured via Breast-Q (1 year)
- Quality of life via EQ-5D

Conclusions

The CRYSTAL–SIX trial investigates cryoablation as a definitive, nonsurgical alternative to breast surgery in early-stage breast cancer. By combining cryoablation, omission of axillary surgery, and ultrahypofractionated radiotherapy, it proposes a modern, patient-centered model.

If non-inferiority is confirmed, this strategy may reduce treatment burden, lower costs, and enhance quality of life without compromising oncologic outcomes.

The SIX trial reflects and may help redefine current standards in de-escalated breast cancer care.

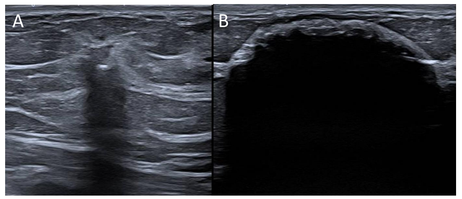


Figure 1. 56 years old. T1N0. A. US-guided cryoablation. B. Ice ball formation

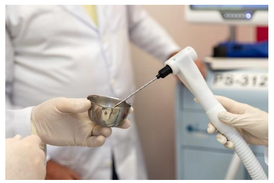


Figure 2. Testing the cryoprobe



Figure 3. Ice-ball formation



Figure 4. Ultrasound-guided procedure



Figure 5. Final procedure

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