Review Article

Cryoablation for breast cancer: a narrative review of advances, clinical applications, and future challenges

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Background and Objective: Breast cancer remains one of the most common malignant tumors affecting women, with its incidence continuing to rise in recent years. Cryoablation, a minimally invasive technique, has emerged as a promising alternative to conventional surgical excision. Its advantages include high precision, rapid recovery, suitability for local anesthesia, and the potential to activate the immune system, making it an appealing option for patients who are either unwilling or unable to undergo conventional surgical procedures. The objective of this narrative review is to assess the progress and current status of cryoablation in the treatment of breast cancer, providing a comprehensive overview of its technological advances and clinical applications, including device development, mechanisms, surgical procedures, indications, and clinical outcomes for different tumour types. In addition, the article discusses the use of cryoablation in combination with immunotherapy and the challenges ahead.

Methods: This study conducted a literature review by searching the PubMed and Web of Science databases to identify the latest research findings in the field of cryoablation technology and breast cancer treatment. Based on these findings, a narrative review was generated.

Key Content and Findings: This article presents the mechanisms, devices, and surgical procedures of cryoablation, affirming its safety and efficacy in the clinical treatment of breast cancer. Additionally, it explores the challenges associated with combining cryoablation with immunotherapy to prevent tumor recurrence. As technological advancements continue, it is anticipated that more extensive clinical trials will be conducted to validate the broader application of cryoablation in breast cancer treatment, addressing the limitations of currently available small-scale studies. This progress will aid in selecting more effective treatment strategies for breast cancer patients.

Conclusions: Cryoablation has been proven to be a unique and effective approach for treating early-stage, advanced, and inoperable breast cancer patients, demonstrating favorable therapeutic outcomes. Additionally, cryoablation can enhance anti-tumor immune responses, and its combination with immunotherapy and nanomedicine shows promise in preventing tumor recurrence. As a result, cryoablation is gradually becoming a viable alternative to traditional surgical methods for breast cancer treatment.

Keywords: Cryoablation; breast cancer; minimally invasive; immune; image guide

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Introduction

Breast cancer is the most common malignant tumor among women. According to the World Health Organization's 2024 statistics, there are approximately 313,510 new cases of breast cancer annually in the United States, accounting for 32% of all new cancer diagnoses among women (1). Although surgical resection is still considered the gold standard in breast cancer treatment, advances in early detection technologies have shifted the treatment paradigm from traditional mastectomy to breast-conserving surgery, which focuses on improving the quality of life (2). While breast-conserving surgery reduces surgical trauma, it still impacts breast morphology, imposing both physiological and psychological burdens on patients.

Cryoablation, as an effective and well-tolerated minimally invasive treatment modality (3), provides an alternative option for patients. This technique employs extremely low temperatures, ranging from −80 to −196 ℃, to induce cellular damage through controlled freeze-thaw cycles, thereby achieving tumor ablation (4). Compared to surgical resection, radiotherapy, and chemotherapy, cryoablation offers advantages such as high targeting accuracy, rapid recovery, ease of local anesthesia, and potential immune system activation (5,6). For patients with early-stage, low-risk breast cancer, cryoablation offers cost-effective and quality-of-life advantages over surgical excision (7). Therefore, cryoablation is an effective alternative treatment for specific patients who are unwilling or unsuitable for traditional surgery, with high patient satisfaction (8).

In 1985, the application of cryoablation for breast tumors was first reported, followed by validation of treatment efficacy through surgical resection and pathological examination, which confirmed the absence of viable tumor cells in the frozen area (9). The introduction of imaging technologies has enabled real-time tracking of the ice ball's location and size during cryoablation, effectively reducing the risk of cold-induced damage to surrounding normal tissues (10). This advancement positions cryoablation as a promising treatment modality.

This review aims to provide a comprehensive analysis of the latest advancements in cryoablation technology for breast cancer treatment, including the most advanced cryoablation devices and procedures. Additionally, it explores the clinical efficacy and applicability of this technology across different patient populations and emphasizes emerging treatment approaches that combine cryoablation with immunotherapy, aiming to offer new insights and innovative treatment options for clinical practice. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1415/rc).

Methods

A literature search was conducted in PubMed and Web of Science databases using the keywords "cryoablation" AND "breast" OR "immune" OR "metastatic breast cancer" OR "abscopal effects". The secondary references cited in articles obtained from the PubMed and Web of Science search were also retrieved. The methodology of the search is summarized in *Table 1*.

Cryoablation devices

Cryoablation devices used in clinical applications are primarily classified into two categories: liquid nitrogen systems and argon-helium systems. The liquid nitrogen systems are based on the principle of phase change refrigeration. Liquid nitrogen, which has a low boiling point, tends to vaporize, a process that absorbs heat from surrounding tissues, forming an ice ball with a maximum long axis of approximately 6 cm and a short axis of 5 cm, thereby freezing the tumor region (11). In contrast, the argon-helium systems are based on the Joule-Thomson effect, where high-pressure argon undergoes throttling expansion through a small orifice into a low-pressure region, while helium, increases in temperature during this process. The alternating cooling and heating cycles in argon-helium systems cause cellular death. The advantage of the Joule-Thomson system is the use of ambient temperature gases, causing temperature changes only at the non-insulated segment of the cryoprobe, which minimizes damage to surrounding normal tissues or the puncture path (12). In state-of-the-art cryosurgery, the liquid nitrogen cryoprobe is gradually being replaced by the Joule-Thomson cryoprobe (13).

Nowadays, medical device manufacturers continue to optimize cryoablation technology to enhance its clinical efficacy. The liquid nitrogen-based ProSense cryoablation system (IceCure Medical, Caesarea, Israel), featuring a unique single cryoprobe, is as effective as a multi-probe system with three cryoprobes for treating the same tumor. Furthermore, the single probe can be repositioned up to three times to treat larger tumors or multiple lesions. ProSense has been utilized in several clinical trials,

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Table 1 Methodology of the search for the review

Items	Specification
Date of search	The first search was conducted on 1/1/2024. The second search was conducted in July, 2024. The last search was conducted on 10/24/2024
Databases and other sources searched	PubMed and Web of Science
Search terms used	"Cryoablation" AND "breast" OR "immune" OR "metastatic breast cancer" OR "abscopal effects"
Time frame	1985–2024
Inclusion criteria	Restricted to articles published in English; without predefined restriction as to the study type
Selection process	M.Y. conducted the article selection

including the ICE3 trial, which has demonstrated positive treatment outcomes and high levels of satisfaction among both physicians and patients (14). The ISOLIS Cryoprobe system (Varian Medical Systems, Palo Alto, USA), combined with the myNeedle laser navigation system (Siemens Healthineers International AG, Steinhausen, Switzerland), employs a 14-G catheter and a sharp cannula design to achieve precise positioning and monitoring of the cryoprobe, ensuring accurate treatment of the target tissue while minimizing damage to adjacent healthy tissues. The V-Probe (Varian Medical Systems, Palo Alto, USA) features a variable-diameter cryoprobe that can be easily adjusted via a sliding button on the handle, allowing the flexible generation of five different cryo zones, giving physicians the ability to tailor the freezing area to meet diverse treatment needs. The ICEfx system (Boston Scientific Corporation, Marlborough, England) integrates i-Thaw™ and FastThaw™ technologies without helium gas heating and includes ten needle ports, making it particularly suitable for handling complex or large tumors, demonstrating significant advancements in cryoablation technology within precision medicine.

Cryoablation mechanism

Cryoablation technology involves the insertion of a cryoprobe into the tumor site and the use of controlled freeze-thaw cycles to induce necrosis and apoptosis of tumor cells, thereby achieving tumor ablation (*Figure 1*). During the freezing phase, the formation of intracellular and extracellular ice crystals, along with changes in osmotic pressure, causes mechanical damage to cell membranes and organelles. Specifically, the freezing process denatures the lipid-protein complexes in the cell membrane, while ice crystals forming inside and outside the cell compromise membrane integrity, leading to a loss of cellular viability that cannot be restored even after thawing. Additionally, low temperatures can cause thickening of the vascular endothelium, resulting in narrowed blood vessels, platelet aggregation, and blood flow stasis, which interrupts the tumor's blood supply and induces hypoxic cell death.

In the thawing phase, the marginal zone of the ablated area experiences sub-lethal cryoinjury that can induce apoptosis. Concurrently, small ice crystals within the cells may recrystallize or fuse into larger ice crystals, exacerbating cellular damage. Furthermore, cryoablation can lead to the release of intact antigens from necrotic cells, thereby triggering an anti-tumor immune response. Studies have shown that following cryoablation, tumor-specific T cells, such as $CD4^+$ and $CD8^+$ cells, as well as natural killer (NK) cells, are increased, along with elevated levels of cytokines like interleukin-4 and tumor necrosis factor-alpha, indicating activating the body's immune response (15-17).

Indication

Patient selection criteria

When determining whether a patient is eligible for cryoablation, several key factors should be taken into consideration. First, cryoablation is most effective for early-stage, low-risk breast cancer patients, particularly when the tumor size is ≤1.5 cm. The procedure shows even better outcomes when the tumor is <1 cm (18). Second, for advanced breast cancer cases, such as those with skin ulceration, distant metastasis, or stage III/IV breast cancer that cannot be treated with traditional surgery, cryoablation can serve as an effective local palliative treatment. This is especially beneficial for patients who do not respond well

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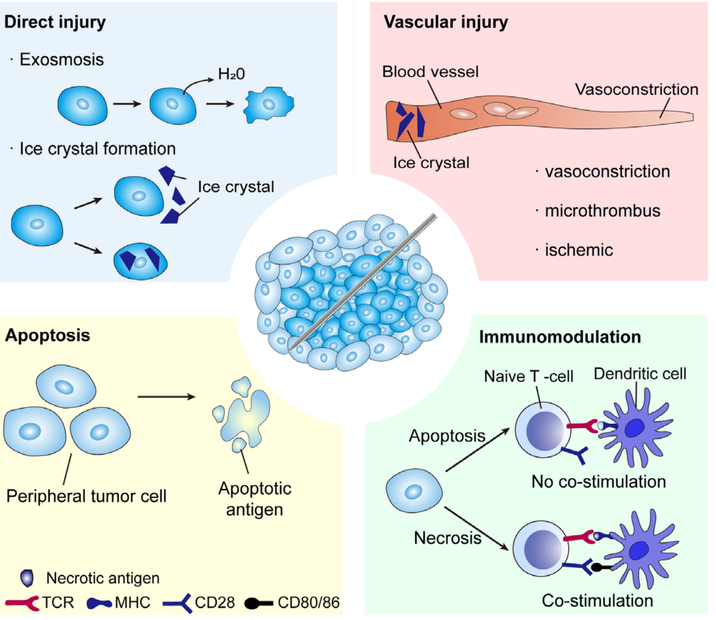

Figure 1 Biological mechanisms of cryoablation. TCR, T-cell receptor; MHC, major histocompatibility complex.

to chemotherapy or radiation therapy. Lastly, given that more than half of breast cancer patients are elderly (19), and considering that those with severe comorbidities, such as cardiovascular or pulmonary insufficiency, may not tolerate the invasiveness and potential complications of surgical excision, cryoablation provides a safe, effective, and minimally invasive alternative for patients who are unsuitable for surgery. This approach reduces the overall burden of surgery, particularly for individuals whose health conditions prevent them from undergoing traditional surgical interventions.

Tumor selection

Cryoablation applies to benign fibroadenomas and certain cases of invasive ductal carcinoma (IDC). For patients with fibroadenomas up to 4 cm in diameter and with significant symptoms, cryoablation is considered an ideal non-surgical treatment option (20). For low-grade IDC, when the tumor is less than 1.5 cm in size, lacking extensive intraductal component, being hormone receptor-positive, and the tumor does not overexpress human epidermal growth factor (HER2), cryoablation becomes a suitable treatment method due to the lower biological aggressiveness and predominantly unifocal distribution of these tumors (21).

Accurate assessment of tumor location is essential for successful cryoablation of malignant lesions. Tumors eligible for cryoablation are those with clearly defined borders on breast ultrasound (US) and located at least 5 mm, preferably more than 1 cm, from the skin surface, chest wall, and pectoral muscles, as the lethal isotherm extends at least 5 mm beyond the observed ice ball on US (22).

Therefore, patients with IDC with extensive ductal components are excluded from cryoablation due to the potential spread of the tumor beyond the ablation margins (23). Invasive lobular carcinoma is also not routinely treated with cryoablation, as its diffuse growth pattern is difficult to accurately assess with imaging techniques (24). Ductal carcinoma in situ (DCIS) often presents with subtle radiopaque microcalcifications, making it initially unsuitable for cryoablation. However, the ability to insert US-visible biopsy markers into the lesion has expanded the potential for cryoablation in treating DCIS. Researchers are currently recruiting patients to assess the efficacy of cryoablation for DCIS (NCT05218044) and are conducting extensive clinical trials to compare the long-term benefits, cost-effectiveness, and therapeutic outcomes of cryoablation versus lumpectomy (*Table 2*).

Procedure

Guided by US, computed tomography (CT), and magnetic resonance image (MRI), the cryoablation probe is placed at the geometric center of the tumor, oriented parallel to the

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Table 2 Clinical trials of cryoablation for the treatment of breast cancer

Items	ACOSOG Alliance Z1072 (NCT00723294)	FROST (NCT01992250)	ICE3 (NCT02200705)	COOL-IT (NCT05505643)	DCIS Cryo (NCT05218044)
Purpose	Exploring the effectiveness of cryoablation in the treatment of breast cancer	Determining the success of tumor ablation in patients undergoing cryoablation and endocrine therapy in patients with early-stage breast cancer	Evaluating the efficacy of cryoablation without lumpectomy and its impact on local and long-term recurrence of early breast cancer	Comparing cryoablation with lumpectomy to assess the impact of cryoablation on disease control, complications, and quality of life	The investigator will evaluate the potential of cryoablation as a minimally invasive alternative to surgery for small areas of DCIS by examining its ability to achieve complete ablation of DCIS within the targeted cryoablation zone of necrosis
Device	Visica 2™ Treatment System	Visica 2™ System	Ice-Sense3™/ProSense™	Endocare SlimLine cryoprobe	–
Enrollment	99 participants (86 were evaluable for the primary endpoint), age ≥18 years	200 participants, age ≥50 years	208 participants, age ≥50 years	256 participants, age ≥50 years	30 estimated participants, age ≥18 years
Tumor type	Tumor size ≤2 cm; unifocal invasive ductal carcinoma; <25% intraductal component	Tumor size ≤1.5 cm; unifocal invasive ductal carcinoma; <25% intraductal component; HR+ HER2−; clinically node negative	Tumor size ≤1.5 cm; unifocal primary carcinoma; ER+ PR+ HER2−	Tumor size ≤2 cm; unifocal invasive ductal carcinoma; <25% intraductal component; ER+ PR+ HER2−	Diagnosis of DCIS by minimally invasive needle biopsy; DCIS spanning ≤2 cm
Interventions	Cryoablation; surgical resection	Cryoablation	Cryoablation	Cryoablation/surgical excision	Cryoablation
Outcome	80/87 (92%) of the treated cancers had a successful cryoablation	–	After a mean follow-up of 54.16 months, the ipsilateral breast tumor recurrence rate was 4.3%, and the breast cancer survival rate was 96.7%	Of the 104 patients followed for almost 2 years, 103 were free of recurrence (>99%)	–

Clinical trials on breast cancer cryoablation can be found at https://clinicaltrials.gov/. HR+, hormone receptor positive; HER2−, human epidermal growth factor receptor 2 negativity; ER+, estrogen receptor positivity; PR+, progesterone receptor positivity. DCIS, ductal carcinoma in situ.

lesion's long axis (*Figure 2*) (8). During the initial phase of the freezing process, particularly within the first 20 seconds, it is crucial to closely monitor the formation of the ice ball. The first freezing cycle is considered complete once the acoustic shadow produced by the cryoprobe fully covers the target area. If the probe's position is suboptimal, the freezing process should be paused, and the probe's position should be recalibrated after the ice ball melts (25). To ensure comprehensive coverage of the tumor and achieve the cytotoxic temperature of −40 ℃, the ice ball should extend at least 10 mm beyond the tumor margin ideally (25-28). When the tumor is adjacent to the skin, a protective barrier can be created by subcutaneously injecting sterile saline or applying a warm compress to the skin surface to prevent frostbite (8). If the tumor is close to the chest wall, elevating the front end of the cryoprobe can help retract the forming ice ball, thus protecting the chest wall (29).

The standard cryoablation treatment consists of two freeze-thaw cycles, and the optimal duration is tissue-specific, depending on factors such as device performance, lesion size, and the required ablation margins. The duration of freezing should be determined based on the physician's expertise in assessing how well the lethal isotherm of the ice ball covers the tumor. Depending on the type of lesion and the composition of the tumor, achieving the necessary coverage may require more or less time.

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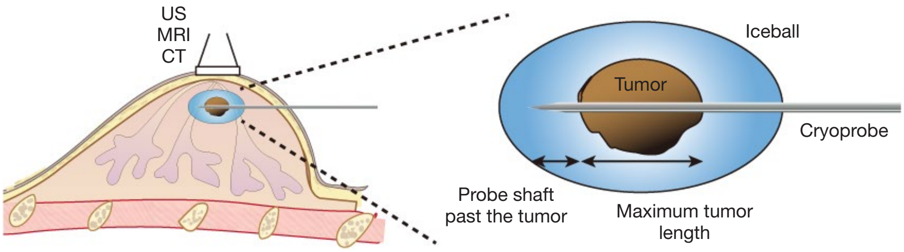

Figure 2 Schematic diagram of cryoablation and cryoprobe position. US, ultrasound; MRI, magnetic resonance image; CT, computed tomography.

Figure 3 A 50-year-old woman was diagnosed with invasive ductal carcinoma and distant metastases. (A) An axial contrast-enhanced T1-weighted fat suppression magnetic resonance image showed the primary breast cancer in the external quadrant of the left breast, measuring 27 mm in its major diameter (arrow). (B) Computed tomography-guided cryoablation of the breast tumor was performed under local anesthesia and conscious sedation. Three cryoprobes and one thermocouple for temperature monitoring were used during the procedure. (C) An axial contrast-enhanced T1-weighted fat suppression image taken 2 months post-procedure showed complete ablation with a large, non-enhanced area due to tissue necrosis, surrounded by a ring of enhanced tissue consistent with granulation tissue in the proliferative phase (arrow). These figures were reused from an open access article (27) and permissions are not needed.

This procedure can be performed in an outpatient setting using local anesthetics, and the cryoablation process itself provides a local anesthetic effect, helping to alleviate pain. Post-procedure, only simple bandaging is required, without the need for sutures. Patients may experience skin bruising, swelling at the puncture site, and pain within the first 24–48 hours after the procedure, but these symptoms typically resolve within three weeks. Any palpable masses usually decrease gradually over the subsequent months (*Figure 3*) (27).

Cryoablation for breast tumors

Clinical experience with cryoablation for breast tumors initially came from the treatment of fibroadenomas, which have an incidence rate of 10%. Numerous studies (29,30) have shown that cryoablation results in a reduction in lesion size and alleviation of pain. Furthermore, the high satisfaction rate observed during one-year follow-up further demonstrates the efficacy of cryoablation, making it an ideal option for treating breast fibroadenomas. Recently, the use of cryoablation in breast cancer has been proposed as an alternative to lumpectomy for small tumors. It has also shown promise as a palliative treatment for advanced, inoperable breast cancer and is suitable for patients who are not candidates for surgery or decline surgical excision. The results have been encouraging.

Early-stage breast carcinoma

With the widespread adoption of screening mammography and increased self-awareness, the detection rate of early-stage breast cancer has significantly increased, sparking interest in the research community regarding the application of non-surgical ablation therapies for early-stage breast cancer (31). Early studies primarily focused on the safety and efficacy of cryoablation, with ablation outcomes needing to be evaluated through postoperative surgical excision. Roca Navarro *et al.* reported that 59 women (mean age 63±8 years) with 60 low-risk unifocal IDC underwent cryoablation before surgery. Pathological examination of the lumpectomy specimens post-cryoablation showed residual invasive cancer in only one of 38 patients with pure IDC and 4 of 22 patients with mixed IDC/DCIS. All treated tumors had clear surgical margins, and no significant procedural complications were reported. Cryoablation effectively eradicates 97% of purely invasive ER+/HER2 tumors ≤2 cm, demonstrating its potential as a patient-specific surgical option (32). Additionally, another study by the team indicated a 95% probability of not detecting residual invasive cell foci in postoperative specimens after cryoablation. Furthermore, the placement of seed markers before the procedure did not affect the cryoablation process or the surgeon's ability to locate the tumor (28). A multicenter pilot study assessed 29 patients with invasive breast carcinomas, visible via the US, and measuring up to 2.0 cm in maximum diameter. Of these, 93% (27 patients) successfully received US-guided cryoablation. Standard surgical excision conducted 1 to 4 weeks post-ablation showed that all tumors smaller than 1.0 cm were completely eradicated. For tumors between 1.0 and 1.5 cm, complete ablation was achieved only in patients with purely IDC without significant DCIS components. For tumors larger than 1.5 cm, the reliability of cryoablation decreased significantly (33). Therefore, meticulous preoperative assessment and intraoperative monitoring are crucial to ensure complete cryoablation of breast tumors.

Most early-stage breast ablation trials had a limited patient cohort, whereas the ICE3 trial, a large multicenter study with 194 participants, concentrated on cryoablation for low-risk small breast cancers. The results indicated that an average follow-up period of 54.16 months, an ipsilateral breast tumor recurrence rate of 4.3%, a breast cancer survival rate of 96.7%, and more than 95% of the patients were satisfied with the cosmetic outcomes (14). The phase II trial by the American College of Surgeons Oncology Group (ACOSOG) for invasive breast carcinoma (mostly ER+/HER2− patients) showed a success rate of 93.8% for tumors <1 cm, 88.7% for low-grade tumors, and 75.9% for tumors <2 cm (34) (*Table 2*).

Metastatic breast carcinoma

Despite the widespread adoption of breast cancer screening techniques, approximately 5% to 15% of patients are still diagnosed with metastatic disease initially (35). These patients often have a poorer prognosis, with a 5-year overall survival rate of less than 30% (36). Compared to early-stage disease, treatment options for these patients are limited. In this context, cryoablation, as a palliative treatment, can effectively alleviate pain, prevent tumor rupture, bleeding, or ulceration, control tumor progression, and potentially improve quality of life and survival.

Beji *et al.* (37) conducted a study on 17 patients with metastatic breast cancer treated with cryoablation, followed by MRI. The results showed that 88.2% (15 patients) achieved complete ablation of the primary lesions with no reported recurrences. The remaining 2 patients, with larger tumors (≥40 mm), experienced recurrences, but their conditions improved rapidly after a second cryoablation. This study indicates that cryoablation is not only an effective palliative treatment for metastatic breast cancer patients but also, due to its good tolerance, low complication rates, and excellent local disease control, particularly suitable for this patient group. Fancellu *et al.* (35) treated 51 stage IV patients with CT-guided cryoablation, where the main metastatic sites were the bones, followed by the lungs and liver, with an average tumor size of 3.32±1.5 cm. The complete necrosis rates of the tumors reached 88.9% and 100% at 2 and 6 months post-treatment, respectively. Six patients (11.7%) with larger tumors required a second treatment. The procedure was well tolerated with no severe complications, and 68.6% of patients experienced minor short-term side effects, such as bruising, edema, and pigmentation. All patients were discharged on the day of the procedure, demonstrating the simplicity and minimally invasive nature of the therapy. Long-term follow-up (average of 60 months) showed only 17.6% of patients had local recurrences, which were successfully re-treated with cryoablation.

Breast cancer unsuitable for surgery

Although breast surgery is generally safe for patients with comorbidities, some individuals may be unsuitable candidates due to general contraindications, primarily related to cardiac or pulmonary insufficiency, or due to the lack of surgical consent (38). Elderly patients with chronic illnesses are particularly at risk for perioperative complications and may be denied surgery as a result (39).

Cazzato *et al.* (40) conducted cryoablation on 23 elderly patients who were not surgical candidates, with a median age of 86 years. After a median follow-up of 14.6 months, 5 patients experienced local recurrence, and 2 of these

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underwent successful repeat cryoablation. MRI follow-ups at 3, 12, 18, and 24 months revealed local tumor control rates of 95.6%, 76.9%, 13.4%, and 9.4%, respectively. Additionally, a retrospective cohort study evaluated the short-term benefits and outcomes of cryoablation in elderly patients with early-stage breast cancer. This study included 35 women over the age of 60 years, with tumors measuring ≤25 mm. Following cryoablation, 2 patients (5.7%) experienced local recurrence, but both responded well to subsequent ablation (41). A separate retrospective study assessed the tolerance, complications, and efficacy of US-guided cryoablation in elderly breast cancer patients aged 80 to 94 years who were unsuitable or refused surgery. Among 25 patients with tumors ranging from 5 to 60 mm, no residual lesions were observed in the first post-treatment US, nor was there any local recurrence during follow-up (6–22 months). Two patients with larger tumors (40–55 mm) required additional cryoablation to achieve local control, and all patients tolerated the procedure well under local anesthesia, with no serious complications reported (42).

These findings suggest that cryoablation is a safe and effective treatment for elderly patients with comorbidities who are not candidates for traditional surgery, particularly in the first year post-treatment. However, tumors larger than 40 mm may require multiple treatments to achieve complete local control.

Cryoablation and immunotherapy

After cryoablation, residual antigenic tissue undergoes coagulative necrosis, leading to the release of nucleoproteins, cytokines, and antigens from tumor cells (43). Thus in addition to its local effects, cryoablation can induce a systemic immune response, with the potential to target metastatic tumors through the immune system (44). A rare phenomenon observed after cryoablation is the regression of distant tumors, known as the abscopal effect. Kumar *et al.* (45) reported a case of a 68-year-old woman with estrogen receptor-positive, progesterone receptor-positive, HER2-negative invasive breast cancer, accompanied by metastasis to two level I axillary lymph nodes. Due to multiple comorbidities and the patient's refusal of standard adjuvant therapy, she was deemed a poor surgical candidate and received cryoablation as the sole treatment. Remarkably, a 5-month follow-up MRI revealed complete resolution of both the primary tumor and the right axillary lymph nodes. Similarly, in a case report by Kaplan (46), a patient diagnosed with stage IV breast cancer underwent cryoablation, which led to the complete regression of hypermetabolic lesions in the left breast, liver, and left axillary nodes after 9 months. Unfortunately, one year postoperatively, the patient developed isolated left axillary lymph node enlargement, which was confirmed by biopsy as recurrent metastatic breast cancer. Although cryoablation can trigger tumor-specific immune responses or a rare abscopal effect, the magnitude and sustainability of this response are often insufficient to eliminate tumors, leading to tumor recurrence and metastasis (47). In particular, cancer cells can evade immune recognition by inhibiting effector T cells through cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) receptors (48). To address this issue, combining cryoablation with immunotherapy may enhance the systemic immune response to reduce tumor recurrence (49).

McArthur *et al.* (50) assessed the application of cryoablation with ipilimumab (CTLA-4) in early-stage breast cancer, confirming the treatment's safety and tolerability without causing surgical delays. The combination therapy group exhibited enhanced immune activation, characterized by elevated levels of Th1 cytokines, increased activation and proliferation of $ICOS^+$ and $Ki67^+$ $CD4^+$ and $CD8^+$ T cells, and a favorable shift in the ratio of effector T cells to regulatory T cells within the tumor post-treatment. Subsequent studies focused on triple-negative breast cancer, exploring the potential benefits of combining cryoablation, ipilimumab, and nivolumab to improve survival rates and boost immune responses (51). Furthermore, Liang *et al.* (52) evaluated the safety and short-term effectiveness of CT-guided cryoablation combined with NK cell therapy and Herceptin for managing HER2-expressing recurrent breast cancer. All adverse effects were manageable and acceptable. The combination therapy not only delivered positive clinical outcomes but also enhanced patients' quality of life, lowered circulating tumor cells, carcinoembryonic antigen, and cancer antigen 15-3 levels, significantly boosted immune function, and notably extended progression-free survival. This study is the first to demonstrate the clinical effectiveness of integrating cryoablation, NK cell therapy, and Herceptin for treating HER2-overexpressing recurrent breast cancer.

However, these trials are limited by sample size and the range of cancer subtypes. As clinical trials combining cryoablation and immunotherapy for breast cancer continue to advance (*Table 3*), multiple studies are underway to

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Table 3 Clinical trial of cryoablation combined with immunotherapy for breast cancer

Items	NCT01502592	NCT03546686	NCT05806385
Title	A pilot study of pre-operative, single-dose ipilimumab and/ or cryoablation in early stage/ resectable breast cancer	A single arm phase 2 study of peri-operative immune checkpoint inhibition and cryoablation in women with hormone receptor-negative, HER2-negative early stage/resectable breast cancer	Local therapy optimization by grouping immune-modulation with cryoablation (LOGIC) for high-risk breast cancers
Aims	Evaluating the safety and tolerability of pre-operative, single-dose ipilimumab and/ or cryoablation in patients with early-stage/resectable breast cancer	Determining the effect of preoperative cryoablation, ipilimumab, and nivolumab on 3-year event-free survival in patients with triple-negative breast cancer after paclitaxel neoadjuvant chemotherapy	Comparing cryoablation alone and cryoablation in combination with pembrolizumab (anti-PD-1/ PD-L1 antibody) with the current standard of care including surgical resection
Enrollment	19 participants, age ≥18 years	80 participants, age ≥18 years	36 participants, age ≥18 years
Tumor type	Invasive adenocarcinoma; tumor size ≤1.5 cm	Invasive adenocarcinoma; ER− PR− HER2− (triple negative); tumor size ≥1.0 cm	Invasive carcinoma; stage I/II cancer; ER−, PR−, HER2− (triple negative)
Interventions	Cryoablation + ipilimumab	Ipilimumab + nivolumab + cryoablation	Cryoablation + pembrolizumab followed by neoadjuvant chemotherapy followed by lumpectomy/mastectomy

Clinical trials on breast cancer cryoablation can be found at https://clinicaltrials.gov/. HER2−, human epidermal growth factor receptor 2 negativity; ER−, estrogen receptor negativity; PR−, progesterone receptor negativity; PD-1, programmed death 1; PD-L1, programmed death ligand 1.

evaluate cryo-immunotherapy regimens for different breast cancer types and stages. These investigations expand our understanding of combined treatment strategies for breast cancer and lay a solid foundation for future personalized treatment protocols.

Innovations in cryoablation combined with immunization

Exploring strategies to enhance the efficacy of tumor immunotherapy shows great potential in utilizing various nanotechnology platforms to boost antitumor immune signals, modulate the immunosuppressive microenvironment, and enhance the body's immune response against tumors, preventing recurrence and distant metastasis. Wang *et al.* (53) innovatively designed a cold-responsive HCPN-CG nanoparticle based on hyaluronic acid, chitosan, poly (N-isopropylacrylamide-co-butyl acrylate), and Pluronic F127, tailored for *in situ* application of cryoablation combined with photothermal therapy in human breast tumors. When the temperature drops below 10 ℃, these nanoparticles disassemble structurally and release the encapsulated drug, synergizing with cryoablation technology to effectively kill tumor cells. Furthermore, Ou *et al.* (54) reported an innovative approach to *in situ* cryo-immunotherapy that relies on cold-sensitive nanoparticles capable of co-delivering chemotherapeutic and immunotherapeutic agents, combined with cryoablation to treat breast cancer. Post-cryoablation, these nanoparticles rapidly release chemotherapeutic drugs and carry small interfering RNA to inhibit programmed death-ligand 1 (PD-L1) expression, promoting dendritic cell maturation and activating $CD8^+$ cytotoxic T cells and memory T cells. This process not only effectively eradicates in suitable patients, but also triggers immune surveillance and clearance of distant tumor cells. Although these experiments are currently limited to preclinical studies in mice, these studies provide critical scientific evidence and practical pathways for enhancing tumor immunotherapy outcomes through precision nanotechnology and cryoablation synergy.

Conclusions

Cryoablation represents a promising advancement in the treatment of breast cancer, offering a minimally invasive alternative to traditional surgical approaches. The development of advanced cryoablation devices and techniques has significantly improved the precision

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and efficacy of this treatment modality. Cryoablation is especially beneficial for certain cases of early-stage breast cancer. It provides a safe, effective option for patients who are either unwilling or unsuitable for conventional surgery.

Future research should continue to explore the potential of cryoablation in combination with other therapeutic approaches, such as immunotherapy, to further enhance treatment outcomes and expand its applicability to a broader range of patients. As technology and clinical experience continue to evolve, cryoablation may become an increasingly integral part of breast cancer management, offering patients a promising alternative with significant benefits in terms of efficacy, safety, and quality of life.

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Footnote

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