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LOCAL-REGIONAL EVALUATION AND THERAPY (DM EUHUS, SECTION EDITOR)

# Ablative Treatment of Breast Cancer; Are We There Yet?

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**Abstract**

**Purpose of Review** Breast cancer treatment has evolved through continuous integration of technological advances and changes in our understanding of tumor biology. Radical mastectomy was the best operation for the technology and beliefs of its time. Advances in technology, the acknowledgement that care is best delivered through a multi-modal approach, and continued investigation have resulted in less disfiguring procedures. Ablative therapy for the treatment of breast cancer is the natural continuation of this trend.

**Recent Findings** Data from breast cancer ablation trials utilizing various energy forms have been favorable and have led to the development of ongoing multi-center treat and observe studies.

**Summary** This paper examines the current status of cryoablation, laser ablation, and focused ultrasound ablation for the treatment of breast cancers. The advantages and shortcomings of each technique are considered and the challenges to be met in order for ablative therapy to become a mainstream clinical treatment of breast cancer are discussed.

**Keywords** Breast cancer · Ablative therapy · Cryoablation · Laser ablation · Focused ultrasound ablation (FUSA) · High frequency ultrasound ablation (HiFU)

## Introduction

The treatment of breast cancer has evolved through continuous integration of technological advances and an improved understanding of tumor biology. Although unthinkable today, radical mastectomy was the best operation for the knowledge and beliefs of its time. Changes in our understanding of tumor metastasis led to modified radical mastectomy. Prospective, randomized data and the acknowledgement that breast cancer therapy is best delivered through a multi-modal approach led to breast conserving surgery becoming the surgery of choice for the majority of breast cancer patients. Advances in technology and continued investigation have allowed for less disfiguring procedures. Ablative therapy is the natural continuation of this trend.

This article is part of the Topical Collection on *Local-Regional Evaluation and Therapy*

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Tumor ablation is a nearly, or completely non-invasive treatment delivered with no incision and can result in near perfect cosmesis. The general concept underpinning ablative treatment is that the in situ destruction of a tumor should result in similar results to the surgical removal of the tumor. Modalities for in situ tumor ablation utilize various energy forms including cryoablation, radiofrequency ablation, laser ablation, microwave thermotherapy, and focused ultrasound ablation. This review will describe the current state of the three most promising techniques: cryoablation, laser ablation, and focused ultrasound ablation.

## Cryoablation

### How Does Cryoablation Work?

Cryoablation induces cell death through alternating freezing and thawing cycles inducing intracellular and extracellular ice crystal formation, osmotic pressure imbalance during thawing, and persistent ischemia due to endothelial cell damage. Cell death occurs by direct necrosis or apoptosis. Cryoablation, similar to other ablative techniques, can induce an anti-tumor immune response which may aid in long-term tumor control [1].

## Description of the Procedure

Cryoablation is usually performed in a supine patient under ultrasound guidance for both probe placement and treatment monitoring. One or more probes, 2 to 4 mm in size, are placed through the skin and into the lesion using local anesthesia (Fig. 1). Cooling of the probe is achieved through the use of liquid nitrogen or argon, and following the freezing cycle, the tissue around the probe is thawed using helium gas or a resistance heater integral to the probe. The "ice ball" created by each probe can be spherical or oblong and up to several centimeters in size and can be visualized in real time by ultrasound (Fig. 2). Typically, two freeze-thaw cycles are performed with the duration of each freeze ranging from 6 to 10 min, and thaw times of 5 to 10 min. Skin overlaying the treatment area can be protected by the placement of warm, fluid filled bags, or injection of room-temperature sterile saline between the ice ball and skin.

## Key Studies

Paplack and co-workers [2] reported on a treat and excise study of 20 patients with breast cancers up to 1.5 cm in greatest dimension. Patients underwent MRI 1 month post-treatment followed by excision. A single cryoprobe was utilized in all patients, placed under US guidance, and the targeted area for treatment included a 1-cm area of normal appearing tissue surrounding the lesion. No anesthesia or sedation was utilized. Eighty-five percent (17/20) of patients had no residual disease at the time of excision. No complications of the treatment were reported. Unfortunately, MRI was found to have poor sensitivity, 0/3 (0%), to detect residual disease.

Simmons et al. [3••] described the results of a treat and excise study (ACOSOG Z1072) of 99 patients with tumors up to 2 cm in greatest dimension. Patients underwent an MRI 14–28 days after cryoablation followed by excision within 28 days of treatment. Probes were placed under US guidance.

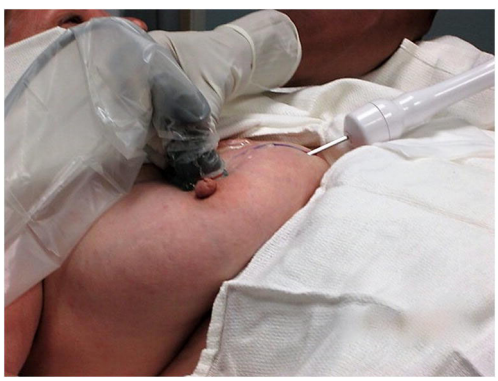

**Fig. 1** Cryoablation probe placed in patient under US guidance (courtesy of Dennis Holmes, MD, Santa Monica, CA)

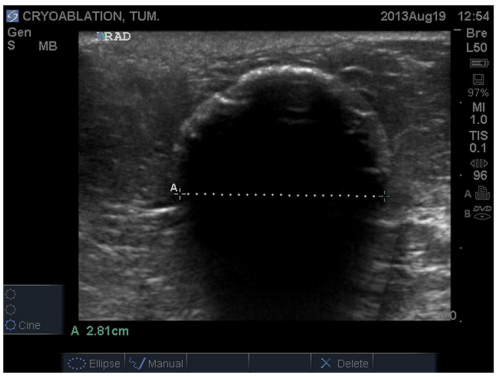


**Fig. 2** Ultrasound image of cryoablation probe demonstrating "ice ball" (courtesy of Dennis Holmes, MD, Santa Monica, CA)

For various reasons, only 87 of the 99 patients enrolled in the study were evaluable. Seventy-six percent (66/87) of patients had no residual disease at the time of excision. Ninety-two percent of patients had complete ablation of the targeted area, and there was 100% ablation in all tumors less than 1.0 cm in greatest dimension. The complication rate was not reported in the manuscript. One key difference between the results of the Paplack and Z1072 study was the sensitivity of post-treatment MRI for the identification of residual viable tumor. The negative predictive value (NPV) of MRI in the Z1072 study was 81.2%.

McArthur and co-workers [4] described the results of an interesting study combining cryoablation with immune therapy. In this pilot study, 19 women with breast cancer for whom mastectomy was planned were treated with pre-operative tumor cryoablation ($n = 7$), single-dose ipilimumab ($n = 6$), or both ($n = 6$). The treatments were generally well tolerated with grade III toxicity seen in only 1/19 patients. In the patients who received the combination of cryoablation and ipilimumab, "Potentially favorable intra-tumoral and systemic immunologic effects were observed with the combination, suggesting the possibility for induced and synergistic anti-tumor immunity with this strategy."

An important advantage of cryoablation when compared to other ablative techniques is the ability to provide it with little or no anesthesia, as the cooling nature of the treatment itself provides analgesia. The primary disadvantage is the limited flexibility to shape the treatment area as it must consist of a multiple of 2 cm or more "ice balls" created by one or more treatment probes. A larger than required treatment area may result in fat necrosis and persistent breast mass (Table 1).

The success of cryoablation in early studies has led to the development of two large ongoing multi-center treat and observe trials: Cryoablation of Small Breast Tumors in Early Stage Breast Cancer (FROST) (https://clinicaltrials.gov/ct2/show/NCT01992250?term=FROST&cond=breast+cancer&rank=1e) and Cryoablation of Low Risk Small Breast Cancer- Ice3 Trial (https://clinicaltrials.gov/ct2/show/NCT02200705?term=ICE3&cond=Breast+Cancer&rank=1).

**Table 1** Comparison of breast tumor ablation techniques

| Technique | Ablation zone characteristics | Benefits | Shortcomings |
|---|---|---|---|
| Cryoablation | | | |
| | • Spherical or oblong<br>• 2 to 4 cm in diameter up to 5 cm in length<br>• Can use multiple probes | • Minimal discomfort<br>• Most clinical data<br>• Ongoing treat and observe trials | • Cost of disposables<br>• Inability to provide sculpted treatment zone<br>• Risk of fat necrosis<br>• Risk of frostbite |
| Laser ablation | • Spherical 2 cm | • Short treatment time | • Cost of disposables<br>• Inability to provide sculpted treatment zone<br>• Risk of skin burn |
| Focused ultrasound ablation | • Multiple small interlaced oblong treatment zones | • Transcutaneous, completely non-invasive<br>• Precise control of treatment area | • Long treatment time<br>• Risk of skin burn |

## Laser Ablation

### How Does Laser Ablation Work?

Laser ablation induces cell death through tissue heating from light energy delivered through a fiber-optic probe. Direct heat injury occurs both at the tip of the probe where tissue is heated to 100 °C, and the surrounding thermal sphere where a target temperature of 60 degrees C is maintained. Following treatment, indirect injury occurs due to tissue vaporization and microvascular damage. The induction of anti-tumor immunity may also play a role.

### Description of the Procedure

The treatment requires the placement of a probe through the skin of the breast and into the target tumor using US, MRI, or stereotactic guidance [5–7] (Fig. 3). Typically, a single probe is used and placed under local anesthesia. In one variant of the technique, a small volume of saline is slowly infused around the laser fiber during treatment to help moderate the temperature at the tip of the probe and prevent tissue adherence. Patients are in the prone position when stereotactic or MRI guidance is utilized and supine when US is used. A multi-sensor thermal probe is placed parallel to the treatment probe at a distance of 1 to 2 cm from the planned ablation zone to provide continuous temperature monitoring in the treatment volume [8••] (Fig. 3). The saline infusion rate can be adjusted and coolant spray maybe applied directly to the skin as needed to mitigate pain and protect against skin burns.

### Key Studies

Dowlatshahi et al. [9] described the results of laser ablation in 54 breast patients who were enrolled in a treat and excise feasibility study. A single saline cooled treatment probe was placed using stereotactic guidance under local anesthesia. Treatment times ranged from 25 to 30 min, and patients underwent surgical excision 1 to 8 weeks later. Mean tumor size was 1.3 cm (range 0.5 to 3.2 cm). Complete tumor ablation was found on final histology of the excised tumor in 70% of patients. Two patient sustained skin burns. No other complications were reported.

Van Esser and coworkers [10] reported on a group of 14 patients with small invasive tumors less than 2 cm in greatest dimension who were enrolled in a treat and excise study. In the operating room, under general anesthesia and immediately following sentinel node biopsy, a single laser probe was placed under US guidance. Laser ablation was performed using an un-cooled fiber and definitive surgical resection directly followed. Mean treatment time was 21.4 min (range 15–30 min). Nicotinamide adenosine diaphorase staining of the excised specimen revealed complete ablation in 7/14 (50%) patients. One patient suffered a skin burn, and a pneumothorax was reported in another.

Schwartzberg et al. [8••] recently reported on the results of a multi-center treat and excise study that enrolled 61 patients with breast cancers up to 2 cm in greatest dimension. Patients

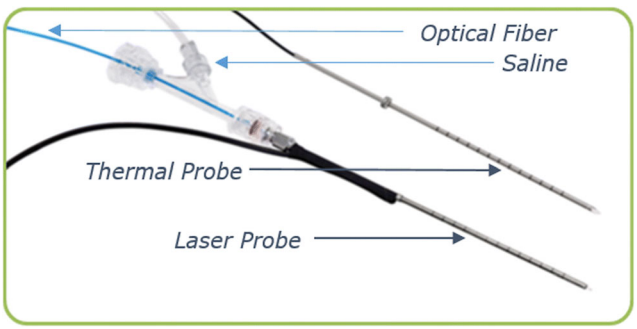


**Fig. 3** Laser probe with multi-sensor thermal probe (courtesy of Barbara Schwartzberg, MD, Denver, CO)

underwent a pre-treatment MRI, followed by laser ablation. A post-treatment MRI was obtained 28 days later followed by surgical excision. The treatment was provided using local anesthesia with ultrasound or stereotactic guidance. A single, saline cooled laser probe and multi-sensor thermal probe were used. Coolant spray was applied to the skin as needed to decrease pain and prevent burns. The mean treatment time was 15.8 min (range 14.5–36.5 min). There were no significant adverse events reported. Two patients developed blisters, there was one hematoma, and three patients developed fat necrosis. All adverse events resolved without intervention. Fifty-one of 61 patients (84%) had complete tumor ablation on pathologic analysis (Fig. 4). Four patients had false-negative findings on post-ablation MRI (Fig. 5). "The negative predictive value of MRI for all patients was 92.2% (95% confidence interval [CI], 71.9–91.9%). Of the 47 patients (97.9%) with tumors 15 mm or smaller, 46 were completely ablated, with an MRI NPV of 97.7%." (Ref 2018) (95% CI 86.2–99.9%).

The high NPV of MRI following laser ablation reported by Dr. Schwartzberg is significant if confirmed in subsequent studies of this and other ablative techniques. The ability to confidently identify patients who have undergone successful ablative treatments will allow for selection of those who require re-treatment with ablation or excision. The high complete ablation rate observed in cancers less than 1.5 cm using laser ablation is promising.

The primary advantage of laser ablation when compared to other techniques is the comparatively short time it takes to complete the therapy. Mean treatment time reported for laser ablation by Dr. Schwartzberg was 15.8 min. This compares favorably to cryoablation which typically takes about twice as long and focused ultrasound which can take over 1 h to perform. Similar to cryoablation, laser ablation is limited in its ability to provide a precisely tailored treatment area, as it is restricted to a single spherical ablation zone. A larger than required treatment area may result in fat necrosis and persistent breast mass (Table 1).

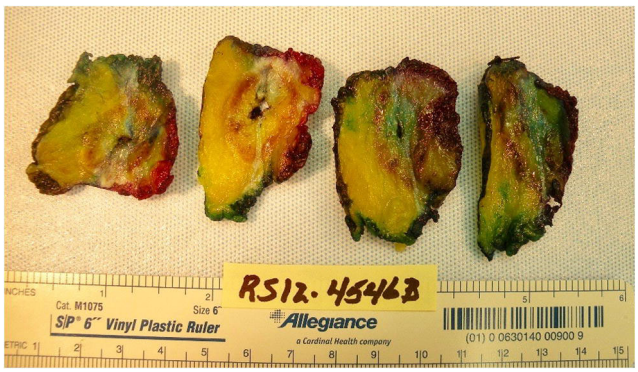


**Fig. 4** Lumpectomy specimen following laser ablation (courtesy of Barbara Schwartzberg, MD, Denver, CO)

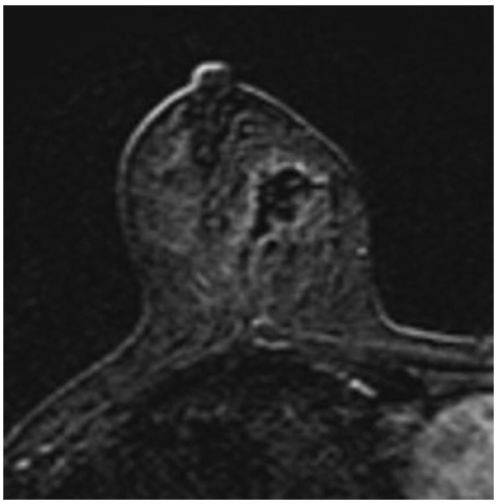

**Fig. 5** MRI following laser ablation demonstrating no tumor enhancement (courtesy of Barbara Schwartzberg, MD, Denver, CO)

## FUSA

### How Does FUSA Work?

Devices designed for focused ultrasound ablation (FUSA) use high power ultrasound waves at low frequencies, between 0.8 and 3.5 MHz. The ultrasound beam is focused at a defined point, passing through the skin and underlying tissues to the focal point, where alternating waves of compression and rarefaction rapidly heat and physically disrupt the target tissue. The energy is typically delivered to a small cigar-shaped target volume measuring up to 6 mm × 15 mm. The location of the treatment zone is precisely controlled, leaving the surrounding tissue unaffected. In order to treat a larger volume of tissue, multiple cigar-shaped sonification zones are arrayed side by side, in the manner of individual pixels, to cover the entire tumor and a small zone of surrounding tissue (Fig. 6).

The tissue in the FUSA treatment zone is subjected to both thermal energy and mechanical stress. Over seconds, focused ultrasound can raise the temperature of the cigar-shaped target volume to over 80 °C [11]. In addition to thermal energy, the rapidly cycling waves of rarefaction and compression at the target zone create micro-bubbles, resulting in intracellular disruption. The end result of these two forces is a precisely controlled zone of coagulative necrosis [12]. Focused ultrasound ablation can be guided via MRI or diagnostic ultrasound imaging.

## Description of the Procedure

### MRI-Guided FUSA

The patient is positioned prone on a specially designed MRI table in which the treatment device is mounted

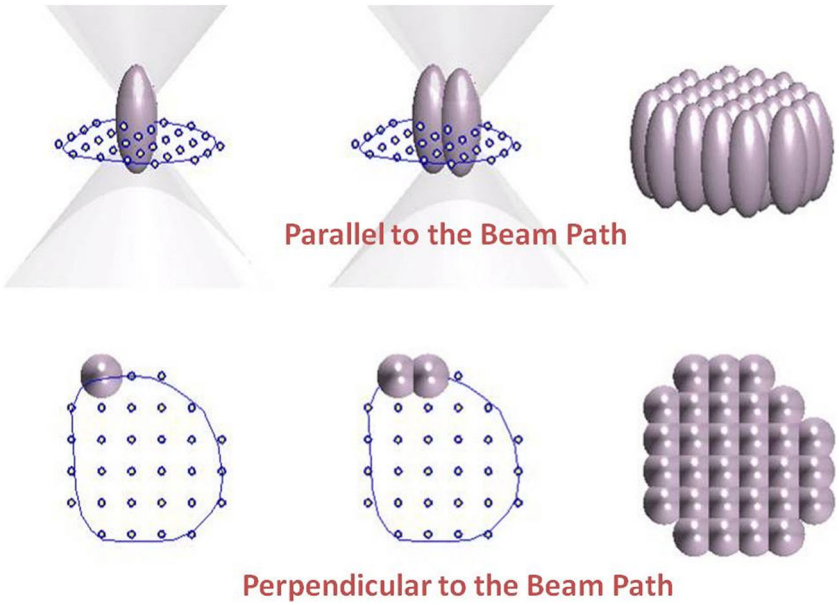


**Fig. 6** Depiction of focused ultrasound ablation treatment plan demonstrating multiple overlapping cigar-shaped sonification zones

(Fig. 7). The breast and surface coil are lowered into a degassed chilled water filled tub containing the ultrasound transducer. Conscious sedation is maintained through the use of an intravenous anxiolytic/analgesic cocktail.

Contrast enhanced MRI images are then obtained. The tumor is identified and the treatment plan is determined. The treatment is then delivered as a series of interlaced elliptical sonication zones delivered within the prescribed treatment area comprised of the tumor and a rim of surrounding normal tissue. The total treatment duration is a function of the number of individual sonification zones required to treat the volume in the prescribed treatment region, typically ranging between 35 and 150 min [13, 14].

Two MRI-directed FUSA devices have been investigated for the treatment of breast cancer, the Sonalleve, Philips Healthcare, Vantaa, Finland, and the ExAblate 2000, InSightec, Ltd., Haifa Israel.


**Fig. 7** The ExAblate device (InSightec, Ltd., Haifa Israel)

## Ultrasound-Guided FUSA

Ultrasound-guided FUSA (USgFUSA) requires the tumor to be clearly visible on ultrasound. The location of the tumor must be at least 0.5 cm from the skin, or chest wall. Most studies of USgFUSA required that the tumor be more than 2 cm from the nipple.

The transducer/imaging device consists of an ultrasound imaging probe situated in a therapeutic ultrasound transducer. This configuration allows for near real-time ultrasound guidance during the procedure. The transducer/imaging device is mounted to an arm that can be moved via servo motors in six dimensions.

The transducer/imaging device is used to obtain images of the breast with the patient in the supine position. The tumor is identified and the treatment volume is determined. The treatment is then delivered to the tumor and a rim of surrounding normal tissue. Conscious sedation or general anesthesia is typically maintained and typical total treatment time ranges between 45 and 180 min [13, 14].

### Key Studies

Gianfelice and co-workers described a series of 12 patients who underwent MRgFUSA using the ExAblate 2000 device followed by resection [15]. All patients had tumors less than 3.5 cm in greatest dimension that were treated to include an estimated normal margin of 0.5 cm. Within 24 days of MRgFUSA, all patients underwent surgical resection. Histology from the first three patients treated in this study demonstrated a mean of 43.3% necrosis of their tumors. Subsequent improvements in the targeting system used on the final nine patients in this series resulted in 88.3% mean

tumor volume necrosis. Two of the final nine patients had no residual viable tumor. Two patients had small second-degree skin burns, four patients reported slight discomfort, and eight reported moderate discomfort on a 3-point scale (slight, moderate, intolerable).

Furusawa and colleagues reported on a study of 30 women with invasive breast cancer less than 3.5 cm in greatest diameter treated by MRgFUSA [16]. The tumor and "at least a 5-mm safety margin of normal tissue" were treated, followed 5 to 23 days later by surgical excision. There were five protocol violations resulting in 25 evaluable patients. Mean tumor necrosis was 98% by volume (range 90–100%). One hundred percent necrosis was observed in 15 patients (60%), and only one patient had less than 95% necrosis of her tumor. One patient suffered a small skin burn. Two patients reported mild to moderate breast pain during sonication.

Dr. Furusawa reported on his experience with MRgFUSA for the treatment of patients with breast cancer at the Second International Symposium on MR-guided Focused Ultrasound [17]. At that time, Furusawa and colleagues had enrolled 47 patients in a prospective single arm trial of MRgFUSA followed by routine whole breast radiation therapy with no excision. All patients had tumors less than 1.5 cm in greatest dimension. Patients underwent ultrasound-guided core needle biopsy of the tumor site 3 weeks after completion of MRgFUSA. If no viable tumor was identified, patients received routine whole breast radiation therapy and were followed with mammography and breast MRI every 6 months. As of October 2010, 47 patients with mean tumor size of 1.1 cm had been treated. The mean treatment duration was 108 min (range 65–209 min). Mean follow-up was 43 months, with no local recurrences or significant adverse events reported.

Napoli et al. [18] treated 10 patients with MRI-guided HIFU using the ExAblate 2000 device. Ten to 21 days post-treatment, patients underwent MRI which demonstrated no residual tumor enhancement in 9 of the 10 patients. All patients underwent routine surgery within 21 days and pathology results demonstrated no residual cancer in 9 out of 10 specimens. No adverse effects were observed.

Ultrasound-guided focused ultrasound ablation of breast tumors has been evaluated in three studies describing the evolution of the technique [19–21].

The first study, published in 2003, described 48 women with tumors up to 5 cm in greatest diameter [19]. Patients were randomized to undergo modified radical mastectomy or USgFUSA followed within 14 days by modified radical mastectomy. Twenty-three patients were randomized to the USgFUSA arm and completed the protocol. The ablation zone included the tumor and a margin of 1.5–2.0 cm around the tumor. Pathologic evaluation of the ablation zone after mastectomy revealed "homogeneous coagulative necrosis, including the [tumor] and normal breast tissue within the target region." No further statistical evaluation of the treatment zone was provided. One of 23 patients (4%) suffered a "minimal" skin burn. Treatment time ranged from 45 to 150 min (mean 1.3 h).

The same group of investigators also described the use of USgFUSA as the primary treatment of breast cancer without excision in a series of 22 patients [20]. Patients had tumors ranging from 2 to 4.8 cm (mean 3.4 cm) measured on ultrasound. All patients received a combination of chemotherapy, radiation therapy, and tamoxifen following USgFUSA. After ablation, patients underwent diagnostic ultrasound evaluation every 3 to 6 months, and ultrasound-guided biopsies at 2 weeks, 3 months, 6 months, and 1 year. All patients were reported to tolerate the treatment well and no complications were observed. No viable tumor was identified on the core biopsies performed within the first year of treatment. Median follow-up was 54.8 months (range 36–72 months). Two of 22 patients developed local recurrence in the treated area, one at 18 months and the other at 22 months after ablation.

A trial studying the combination of focused ultrasound ablation with immunotherapy for the treatment of stage IV breast cancer is underway at the University of Virginia [22]. This study is evaluating the combination of ultrasound-guided focused ultrasound ablation using the Echopulse (Theraclion, Paris) (Fig. 8) and immunotherapy to treat patients with stage IV breast cancer. Focused ultrasound has been demonstrated to result in tumor antigen exposure and presentation to dendritic cells, thus acting as an auto-vaccine. Pembrolizumab is a PD-1 targeted antibody used in the treatment of multiple solid tumors to augment T cell activation. It is hypothesized that the combination of these two modalities will result in T cell infiltration into breast tumors, as well as systemic immune responses.

Focused ultrasound ablation is an entirely transcutaneous treatment, requiring no placement of skin penetrating probes. The truly non-invasive nature of this treatment, along with precise treatment control afforded by near real-time monitoring of each small sonication zone in the treatment plan, is its main advantages when compared to other ablative techniques. Long treatment times required by the current generation of devices, up to 2 h, is its main detraction (Table 1).

## The Future of Ablative Therapies for Breast Cancer Treatment

If any of the current ablative techniques are demonstrated to be equivalent to breast preserving surgery in the treatment of patients with small breast cancers, there are still three significant concerns to be addressed prior to its clinical implementation: detection of residual tumor on imaging, duration of treatment, and persistent breast mass after ablation in some patients.

The ability to accurately detect residual tumor following therapy will be required if ablative therapies are to be used

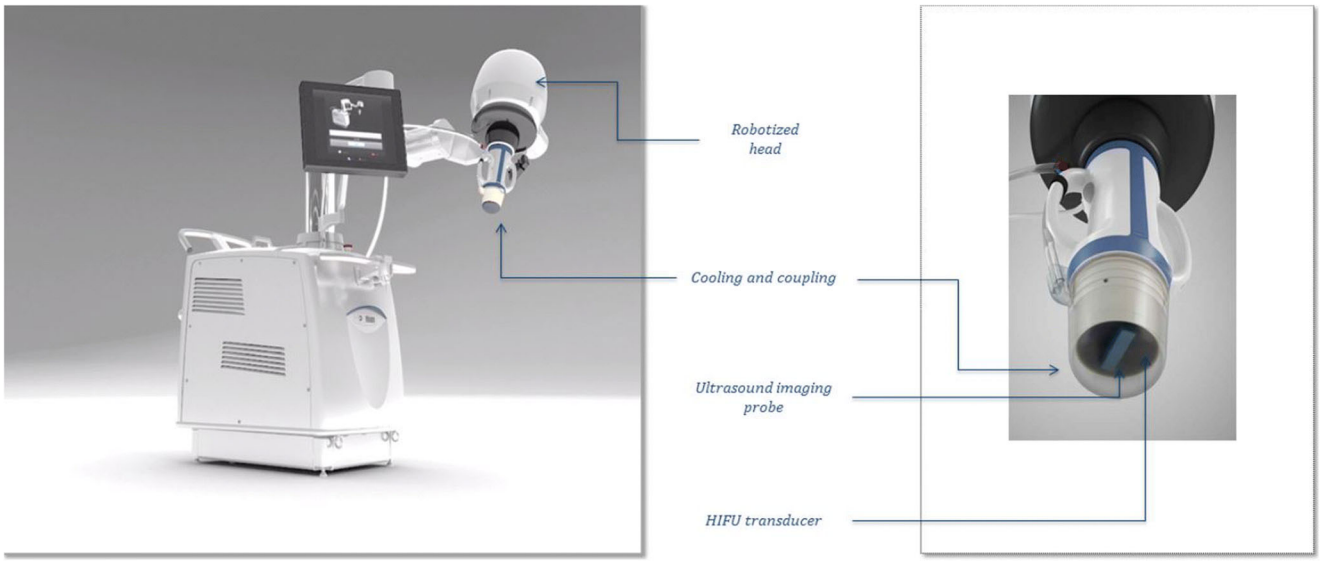


**Fig. 8** The Echopulse device (Theraclion, Paris)

to treat breast cancer. Recent findings demonstrating the ability of MRI to document post-ablation success are highly encouraging. Schwartzberg et al. found a 92% negative predictive value of MRI to detect residual viable tumor in their laser ablation study [8]. Hopefully their results will be replicated in future studies of laser therapy and other ablative techniques. If so, when residual tumor is detected on MRI following ablation, it can simply be targeted for re-treatment, similar to a patient with a positive margin undergoing re-excision lumpectomy.

Long treatment times are currently required for FUSA. The most recently presented data on MRgFUSA reported median treatment duration of 108 min (range 65–209 min) [17]. Total treatment time must be reduced before MRgFUSA can compare favorably to the operative time of lumpectomy. The most commonly used MRgFUSA device for breast cancer treatment and research, the ExAblate 2000 (InSightec, Ltd., Haifa Israel), is at best a general purpose device. It is utilized to treat a variety of organs including the uterus, breast, prostate, brain, and bone. If studies demonstrate FUSA to be equivalent to breast preserving surgery, it is likely that specialized multiple transducer breast specific treatment devices will be developed, with the potential to substantially reduce treatment times. A dedicated MRgFUSA breast treatment device is currently under development, the Sonalleve-based prototype (Philips Healthcare, Vantaa, Finland) which is integrated into a 1.5-T MR scanner [23•].

Fat necrosis, resulting in a persistent palpable mass, can occur in patients following ablative therapy. A persistent breast mass can be anxiety provoking to both the patient and her surgeon along with the potential to obscure locally recurrent disease. While breast imaging can minimize the likelihood of a missed local recurrence, fat necrosis following ablative treatment of breast cancer may prove to be a significant challenge to the widespread adoption of ablative techniques. However, the prevention and management of persistent palpable masses following ablation has yet to be examined and may be amenable to systemic or local pharmacologic therapy. In the worst case, the minority of patients who develop a persistent, problematic post-ablation breast mass could simply undergo surgical excision.

Ablative treatments of breast cancer have been studied in several relatively small trials. To date, these studies have demonstrated the various approaches to be safe, but the ability to provide complete tumor ablation has ranged widely. Treat and observe studies are ongoing using cryoablation and FUSA in highly selected patients. A trial studying the combination of focused ultrasound ablation with immunotherapy for the treatment of stage IV breast cancer is underway at the University of Virginia [24]. A treat and observe study of interstitial laser therapy is currently under development [25].

## Conclusions

Breast conserving therapy has been extensively studied and is without question the current “gold standard” for the treatment of patients with small breast cancers. Breast conserving surgery has been widely adopted because it is a brief procedure with low morbidity that can be usually accomplished without genteral anesthesia. It provides exceptional local control, and in experienced hands, most patients can expect good to excellent cosmesis. Breast conserving surgery requires minimal technology and can be successfully employed in most settings. In comparison, ablative therapies require complex technology with very limited availability. Treat and observe studies of ablative therapies addressing local failure rates, cosmesis, cost-effectiveness, and long-term patient

satisfaction are ongoing, and it is likely that ablative cancer therapies will become commonplace in the future. Ablative treatment of breast cancer has clear advantages. Given comparable results, few individuals would choose to undergo surgery if there are other similarly effective options.

## Compliance with Ethical Standards

**Conflict of Interest** David Brenin reports grants from Theraclion during the conduct of the study for research support.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
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