EXPERT REVIEWS

# High-intensity focused ultrasound in breast pathology: non-invasive treatment of benign and malignant lesions

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Breast neoplasms are one of the leading causes of morbidity and mortality in women. Even if surgery is the treatment of choice, other forms of less invasive radical treatment are desirable. High-intensity focused ultrasound is already established as a valid non-invasive technique that ensures tumor ablation in various organs. The use of ultrasound or magnetic resonance guidance allows having some advantages such as the capability to treat tumors in moving organs or the possibility to have a real-time monitoring of the temperature increase. The aim of this paper is to report the use of high-intensity focused ultrasound technique with ultrasound and magnetic resonance guidance for the ablation of breast tumors, including both benign and malignant lesions.

**KEYWORDS:** breast diseases • fibroadenoma • high-intensity focused ultrasound ablation • invasive ductal carcinoma • magnetic resonance imaging

Breast tumors, either benign or malignant, are commonly diagnosed during screening imaging procedures. Treatment options include follow-up for small, likely benign lesions, or biopsy when imaging criteria are not conclusive. Surgery is the treatment of choice for malignant lesions and larger/growing benign tumors.

Several trials have reported that breast surgery, either conservative or radical, can be considered a safe and effective first-line treatment for early breast cancer, with a long-term survival rate substantially superimposable between women who undergo breast-conserving surgery and radical mastectomy [1,2].

Percutaneous ablation techniques have been investigated previously for the treatment of breast tumors, including radiofrequency ablation (RFA) and cryoablation, but presently there are very few literature reports on their clinical efficacy [3].

High-intensity focused ultrasound (HIFU) is a noninvasive ablation technique that produces thermal tissue necrosis by using sonic energy. Clinical applications of HIFU include ablation of uterine fibroids, bone primary and metastatic lesions, breast, prostate and abdominal solid tumors [4–7], either under ultrasound (US) or under magnetic resonance (MR) guidance.

The aim of this paper is to review the technical principles of HIFU for the treatment of benign and malignant breast lesions and to report our preliminary clinical results.

## Technical principles of HIFU ablation

HIFU is an effective, noninvasive ablation technique for the treatment of benign and malignant tumors in various organs/tissues.

A piezoelectric transducer located inside the MR table/US scanner generates a high-frequency/high-intensity ultrasonic beam directed to a precise focal spot inside the targeted tissue, causing a rapid increase of local temperature. In order to determine protein denaturation and consequent cell death, tissue exposure must exceed a temperature threshold (56°C maintained for at least 1 s). Then, high temperature levels will cause cell death



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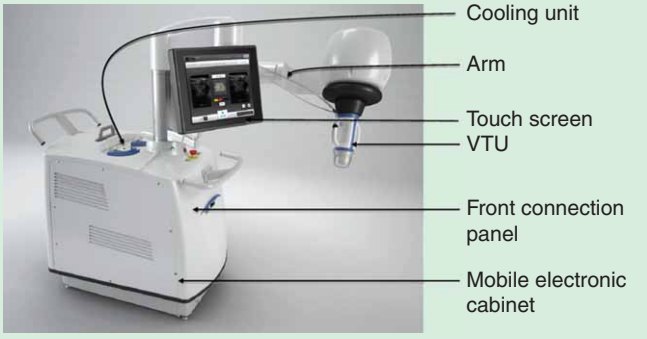


**Figure 1. Ultrasound-guided focused ultrasound ablation device (Echopulse, Theraclion).**
VTU: Visualization and treatment probe.

in a very short time, while lower temperature levels should be prolonged for more seconds (e.g., 50°C should last for at least 10 s) in order to obtain the same ablation effect.

Owing to the very precise focusing of the US beam, this technique allows accurate and safe thermal ablation of the target tissue without causing damages to surrounding anatomical structures.

In the past decade, different minimally invasive techniques have been proposed for the treatment of early-diagnosed breast cancers, with promising results (RFA, interstitial laser ablation, cryotherapy, etc.). RFA is one of the most investigated techniques in this field. With the exception of cryotherapy, all the listed techniques act by causing a rapid increase of temperature within the target tissue, resulting in damage to cell's membrane and consequent coagulation necrosis. Cryotherapy has the same results, but it produces a rapid decrease of temperature (from -185 to -70°C) with an iceball growth [3].

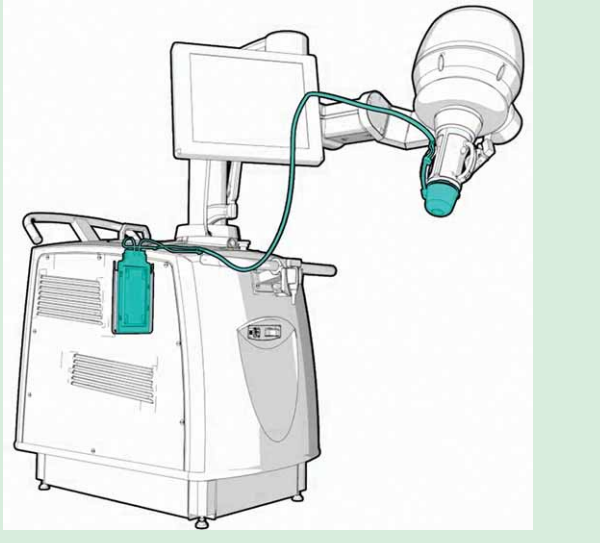

**Figure 2. Device's set-up used to remove air bubble from the circulating water and enable consequent wave transmission and skin protection during the treatment.**

Contrary to the described mini-invasive techniques that provide the introduction of a variable number of needles inside the target tissue with focal skin incisions, focused US ablation is completely noninvasive and fully extracorporeal since the HIFU beam is generated by an external transducer. Minimally invasive ablation modalities and, in particular, RFA use US guidance because they typically operate with frequencies that can potentially interfere with MR sequences and produce significant artifacts. HIFU can benefit also from the MR guidance, exploiting many of its advantages during the entire procedure, from the planning to the evaluation of produced effects.

## US-guided focused US ablation

### *US guidance*

Conventional US has been successfully used as guidance modality for HIFU ablation in various organs, including pancreas, liver and other abdominal organs [7]. US-guided focused ultrasound ablation (USgFUS) is significantly cheaper than MR-guided focused ultrasound (MRgFUS), but its true advantage is represented by the capability to guide treatments in moving organs, owing to the real-time imaging capability, not degraded by respiratory movements; this feature is very useful when treating breast nodules, due to the movement of rib cage during breathing.

### *USgFUS technique, patient positioning & clinical indications*

The USgFUS device (Echopulse, Theraclion, Malakoff – France) has received the CE mark in 2013 for treatment of breast fibroadenomas and thyroid nodules. It is composed of an electronic cabinet, a visualization and treatment probe, mounted on an arm and moved by motors, and an imaging system, with an US scanner integrated into the device (Figure 1).

Similarl to MRgFUS, a cooling and coupling set is used to enable wave transmission and to protect the skin during the treatment (Figure 2).

During treatment, the patient lies in a supine or lateral position with the breast immobilized using a dedicated device. After positioning the visualization and treatment probe in front of the target lesion, the operator manually defines the target treatment volume as well as the skin layer to be protected. A laser system pointing near the target lesion is also used to check any patient motion and to immediately stop the sonication if a significant movement is detected. Based on lesion location and size, the operator can decide to treat different parts of the nodule.

In order to avoid thermal damage to the skin or the pectoralis muscle, a safe distance of at least 5 mm from these structures must be maintained. The spot sonication dimensions are 2 mm in thickness and 9 mm in length. US beam can be focused at a minimum distance of 11 mm and a maximum distance of 23 mm. Thus, the ideal target lesion should be at least 9 mm thick and should be at a distance between 14 and 26 mm from the skin.



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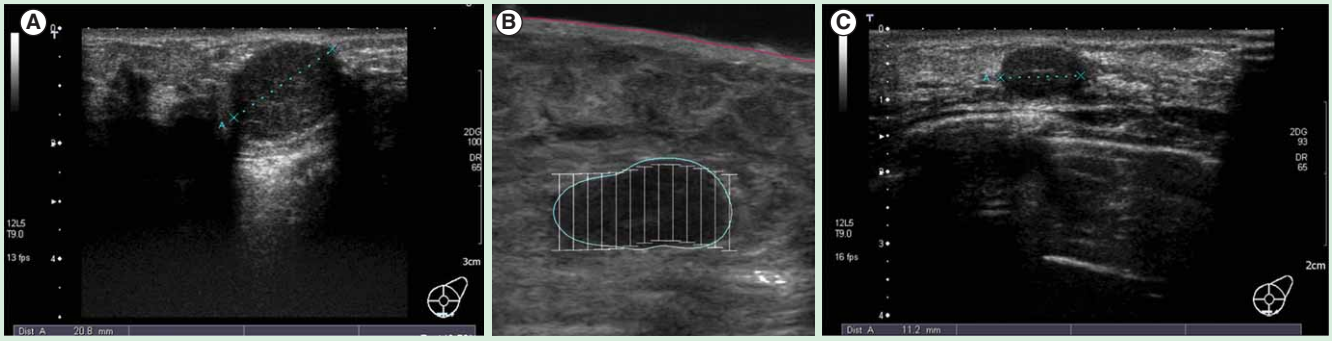


**Figure 3. USgFUS of breast fibroadenoma. (A)** Ultrasound image acquired on a transversal plane shows a 20-mm fibroadenoma located between the inferior quadrants of the left breast. **(B)** After manually defining the skin line (red line) and fibroadenoma borders (blue line), the system automatically generates the sonications (white lines) in order to cover the entire volume of the target tissue. **(C)** The 3-month US follow-up shows a 50% reduction of the fibroadenoma (10 mm of maximum diameter).

The energy dose that can be delivered over the procedure must be adapted to each patient and can range from a minimum of 82 J to a maximum of 249 J. At the beginning of the treatment, a test sonication is performed, with the energy progressively increasing until a hyperechoic mark is visible inside the target area. Once the correct level of energy is established, the treatment can start and the system automatically moves the focal point to each planned sonication.

### *Evaluation of treatment efficacy*

Unlike MRgFUS, US guidance does not allow a quantitative evaluation of thermal accumulation within the ablated tissue or the adjacent structures.

Anyway, a qualitative depiction of the tissue damage can be obtained by the increase of tissue echogenicity at the level of the focused beam.

Rabkin *et al*. tried to determine the mechanisms and bioeffects involved in the development of the hyperechoic spots by measuring temperature changes, cavitation activity and echogenicity in an US image during 10 s HIFU exposures of a pig skeletal thigh muscle *in vivo*. They found that bubbles are present at the site of HIFU treatment during the appearance of a hyperechoic region in B-mode US images and that cavitation activity is involved in the development of hyperechoic regions at the HIFU focus [8]. Although, in literature, different studies establish a good correlation between intra-operative assessment of USgFUS ablation and MRI follow-up or histopathology [9,10], the precise mechanism of echo increase still remains unclear.

Contrast-enhanced (ce) US imaging with micro-bubbles or nano-bubbles has been used for assessment of treatment efficacy [11,12] by providing pre-treatment imaging, enhancing cavitation and evaluating effects of thermal ablation during and after the procedure [13].

### *USgFUS of benign breast lesions: background & personal experience*

So far, the literature still lacks data about USgFUS treatment of fibroadenomas, and just a single article has been published [14]. about the use of MRgFUS for the ablation of this type of lesions. In this article, Hynynen *et al*. evaluated the feasibility of MRgFUS in treating 11 histologically proven and device-accessible breast fibroadenomas, with 8/11 lesions demonstrating complete or partial lack of contrast material enhancement.

A different CE-approved USgFUS device (Model-JC HIFU system, Chongqing Haifu, China) is currently available for ablation of different neoplasms, including breast lesions. However, the current published data [15,16] are focused only on treatment of malignant tumors, showing very promising results (5-year disease-free survival of 95%), although, to our knowledge, no data have been reported about the use of this device for the treatment of breast fibroadenomas.

Therefore, our paper is the very first report focusing on the ablation of breast fibroadenomas with US-guided focused USs.

From October 2013 to April 2014, 10 female patients (age range: 18–34 years old, average: 26) with cytological/histological diagnosis of single or multiple fibroadenomas of at least 1.5 cm in maximum diameter have been enrolled in the study. After giving their informed consent, all the patients have been treated on an outpatient basis; for all procedures, a local anesthesia (10 mg of 2% lidocaine) with mild conscious sedation (midazolam 2 mg) has been used. In two patients, bilateral procedure was performed during the same session, with a total of 12 fibroadenomas treated so far. The maximum diameter of fibroadenomas ranged between 19 and 44 mm (median: 26.5 mm). The number of sonications ranged between 54 and 148 (mean: 88). The mean duration of the entire procedure, including in-room and out-room time, was 136 min (range: 80–210 min), while the average time from the first to the last sonication was 57.2 min (range: 40–100 min). In one patient, we used 199 J of energy with sonication duration of 7 s; in all remaining patients 102–128 J energy (sonication duration: 3–4 s) was sufficient to obtain ablation tissue. The mean total delivered energy was 115.94 J/site. None of the patients felt pain during treatment; if patients reported a local complaint, the administered energy was reduced to the lower level.

After the procedure, each patient was monitored for 2 h prior to discharge.




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At 3 month follow-up, all treated fibroadenomas showed volumetric reduction, with 50% reduction of the maximum diameter of the fibroadenomas (10–20 mm) (Figure 3). No adverse events were recorded during the follow-up period, except a mild swelling and hardness of the treated area. A non-steroidal anti-inflammatory drug was administered for the first day after the treatment to all patients in order to reduce the edema in the treated area, but none of the patients reported any type of pain during the whole follow-up period.

Compared to the MR guidance, USgFUS of breast fibroadenomas showed some advantages: a shorter procedure duration, more comfortable patient positioning that avoids large movements during the procedure and the absence of contrast agent performed before/after the treatment.

Even without precise temperature monitoring, the presence of hyperechoic spots can be safely considered as ablation effect of the focused US beam.

## MRgFUS

### *MR guidance*

Currently, MRgFUS has CE mark and is approved as alternative treatment for uterine fibroids and bone lesions. Its use for the ablation of breast benign and malignant lesions is still under evaluation [17].

The MR guidance represents an added value for the safety and efficacy of HIFU in breast lesions, thanks to several advantages. First of all is the use of intravenous contrast agent: in fact, contrast-enhanced MRI of breast shows the highest levels of sensitivity for detecting breast nodules among the other imaging techniques that are currently available [18–20], with sensitivity levels ranging between 89 and 100%. The capability of the ce-MR in depicting tumors allows precise planning at the start of the procedure and accurate evaluation of the treatment efficacy at the end of the procedure.

The second added value is represented by temperature monitoring, a valid and established method for precise and real-time intra-procedural evaluation of temperature increase measured within the treatment area as well as the surrounding tissues. The most used method is represented by the proton resonance frequency (PRF) shift technique: it is based on the temperature dependence of the water proton-resonance frequency shift, which approximately corresponds to 0.01 ppm per degree Celsius [21–28]. Usually, phase-difference fast spoiled gradient-echo sequences are acquired to provide temperature-dependent images and real-time mapping of the thermal dose on a preferred imaging plane during MRgFUS treatment. During the MRgFUS procedure, the temperature-sensitive MR sequence provides a closed-loop control of energy deposition, with a temperature accuracy of 1°C, a spatial resolution of 1 mm and a temporal resolution of 3 s. At the start of the treatment, the system automatically sets up the parameters of the sonication. Based on the local energy deposition and heat conduction, after each sonication, sonication parameters (energy, power and frequency) can be potentially adjusted in order to reach the desired temperature within the focal point. The main limit of the PRF shift method is represented by the lack of capability to correctly measure the temperature within the fat tissue, since there is no hydrogen bonding among the methylene protons that supply the bulk of fat signal [29]. This is very important to underline when treating breast tumor because of the high representation of fat tissue in breast anatomy, and most of all in post-menopausal women. Thus PRF-shift method is very useful in order to have quantitative measurements of the temperature reached when treating inside the nodule compared to the borders of the lesion or to surrounding safety margins.

When treating the tumor borders as well as normal-appearing safety margins, other sequences can be used as a different type of thermometry. The presence of fat tissue represents the main limit for a correct measurement of temperature increase; therefore, different types of sequences are still under evaluation. T1- and diffusion-weighted imaging has been tested for temperature imaging, and they have been able to show the location of the hot spot in tissue [30–32]. Using this type of sequence, a qualitative measurement of the temperature increase can be obtained in tissues with prevalent fatty composition. Most investigators have focused on measuring the change in the signal magnitude of a T1-weighted sequence [33,34]. A spoiled gradient echo (GRE) sequence is implemented with flip angles alternating between two values every measurement. The phase information is extracted after every time frame and is used for PRF-based temperature measurements in aqueous-based tissues. The magnitude signal from two consecutive time frames is taken to calculate T1 values in adipose tissue using the variable flip angle method [35,36]. In this way, T1-based temperature measurements can be obtained in adipose tissue without affecting the PRF-based temperature measurements used for aqueous tissue. Finally, also apparent T2-based temperature mapping has been proposed in a recently published study conducted on a porcine model, allowing for the monitoring of the temperature in the subcutaneous adipose tissue layers [37].

### *Evaluation of treatment efficacy*

Similar to the process of lesion identification, the use of ce sequences represents a significant advantage also for the evaluation of post-treatment changes. The ce GRE T1-weighted sequences with subtracted images allow a rapid visualization and estimation of the ablated area, providing an early view of the treatment efficacy. In the current literature, most of the studies focusing on breast cancer ablation with HIFU have been conducted as pilot feasibility and safety studies. In these initial studies, treatment efficacy was evaluated with histopathology results obtained from surgical resection of the ablated area and showed variable complete ablation rates ranging from 24 to 100% [38]. In 2007, Furusawa *et al.* [39] performed breast cancer ablation with MRgFUS and evaluated treatment efficacy with only clinical and imaging follow-up for a median period of 14 months. Of the 21 treated patient, four patients underwent a second treatment and only one recurrence was observed. Finally, Wu *et al.* [15] followed up the enrolled patients with

radiological and pathological assessment and long-term evaluation for local recurrence.

### *MRgFUS of malignant breast tumors: background & personal experience*

Breast cancer treatment has changed over time from radical mastectomy to conservative, minimally invasive procedures. This has been possible thanks to the association between screening protocols and the widespread use of several recent techniques such as breast tomosynthesis or ce-MR studies that provide early diagnosis of very small tumors [40–42]. Even if the clinical use of MRgFUS for the treatment of breast cancer is still waiting for CE and US FDA approval, it could be speculated that its noninvasiveness makes this treatment more psychologically and cosmetically acceptable to patients and more suitable for treating patients who are at high risk for surgery. Since 2001, several studies have been published in literature on the safety and efficacy of MRgFUS breast cancer treatment, with a patient population ranging from 1 to 22 and showing relatively limited efficacy at surgery [43–48].

In our department, 10 patients with biopsy-proven single focus of invasive ductal carcinoma were enrolled in a 'treat and resect' nonrandomized multicentric study.

None of the patients had personal or family history, suggesting a greater than average likelihood of a *BRCA1* or *BRCA2* gene mutation. The main criteria for genetic counseling were established according to the literature [49].

Patient's risk factors and pathology data are respectively listed in Tables 1 & 2.

All the patients underwent core-needle biopsy (Tru-Cut) in order to confirm the ductal histotype of the tumor and also to evaluate the immunohistochemistry for establishing the post-surgical drug therapy. Moreover, there must be no evidence of suspicious axillary lymph nodes at imaging (x-ray mammography/US/ce-MRI).

Main inclusion criteria were the dimensions (<20 mm) and the location of the lesion that should be at least 15 mm distant from both skin and pectoral muscle.

After 10–21 days post-treatment, all the patients underwent follow-up ce-MRI; surgical resection was planned within 14 days after MR follow-up.

With the local ethics committee approval and after patients' informed consent, all the treatments were performed on a 3T scanner featuring a 208-element annular phased-array focused US transducer embedded into the MR patient table (ExAblate 2100, InSightec, Haifa, Israel). During the treatment, patients were lying prone with the breast located within a dedicated breast coil filled with degassed water. A mild conscious sedation was performed in all cases. 3D fat-sat T1 GRE acquired on three planes without and with contrast administration as well as subtracted images were used to confirm the correct positioning of the lesion compared to the transducer and also used to plan the treatment. Planned sonications had a 30% superimposition to each other in order to have a complete cover of the nodule and of the 5 mm-safety margins. The average lesion dimension was 12 mm. The mean level of energy used ranged between 1792 and 1875 J. The mean sonication number was 50, with a sonication duration fixed at 40 s. A low power range (<50 W) was used in all cases to avoid tissue cavitation and consequent unpredictable effects on the tissue.

The average treatment time was 2 h and 20 min (range: 1h and 20 min to 3 h).

Both PRF and longitudinal relaxation time (T1) were acquired at each sonication and used for temperature monitoring; in particular, PRF sequences were considered when sonicating inside the solid tissue, while the T1 difference calculated by subtracting the phase before the sonications from the phase during the sonications were considered when sonicating inside the fat tissue to obtain the temperature elevation.

In order to reduce as far as possible the potential errors in measuring the exact temperature within the sonication spot [50], patients were asked to breathe as regularly as possible, without taking in deep breaths. Moreover, the prone position and the presence of two bands narrowed around the patient's chest and abdomen minimized the gross motion of the breasts.

No adverse events were recorded during or after the procedure. At the end of each treatment, all the patients were monitored for 2 h prior to discharge.

**Table 1. Patient's risk factors.**

| Race | Caucasian (10/10) |
|---|---|
| Parity | 1/10–none<br>2/10–1 pregnancy<br>7/10–>1 pregnancy |
| Living children | 9/10 |
| Age at first conception | Mean age 28.5 (24–32) |
| Exposure to hormonal therapy | 0/10 |

**Table 2. Patient's pathologic data.**

| | ER (%) | PR (%) | HER2/neu (%) [score] | Ki 67 (%) |
|---|---|---|---|---|
| Patient 1 | 90 | 40 | Neg [0] | 1 |
| Patient 2 | 90 | 60 | 10 [1+] | 4 |
| Patient 3 | 70 | 70 | Neg [0] | 65 |
| Patient 4 | 80 | 70 | Neg [0] | 14 |
| Patient 5 | 70 | 0 | Neg [0] | 15 |
| Patient 6 | 95 | 80 | 20 [1+] | 13 |
| Patient 7 | 95 | 30 | 12 [2+] | 28 |
| Patient 8 | 80 | 20 | 25 [1+] | 6 |
| Patient 9 | 82 | 68 | 18 [1+] | 8 |
| Patient 10 | 78 | 48 | 14 [2+] | 30 |

ER: Estrogen receptor; PR: Progesterone receptor.


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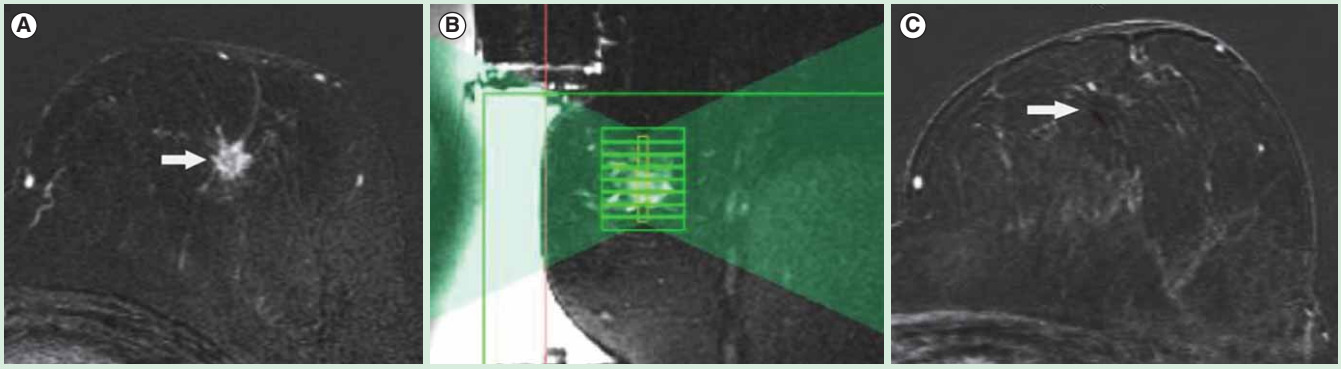


**Figure 4. MRgFUS of breast invasive ductal carcinoma. (A)** Subtracted 3D gradient echo T1-weighted axial image acquired after gadolinium injection shows a small rounded nodule of invasive ductal carcinoma between the upper quadrants of the left breast (arrow). **(B)** T1-weighted sequence acquired on a sagittal plane shows the predicted ultrasound beam path (green triangles) with the planned sonications (green boxes). **(C)** The same sequence acquired after magnetic resonance-guided focused ultrasound treatment shows the ablated area, without residual cancer enhancement (arrow).



All the patients underwent partial breast resection (lumpectomy) and sentinel axillary lymph node resection; in all cases, histopathology confirmed the presence of clear surgical margins of the treated area in the breast, then there was no need for the patients to undergo a surgical enlargement. In 6/10 of patients (60%), no enhancement was seen on breast ce-MRI performed 10–21 days post-treatment (Figure 4) and pathology confirmed the presence of coagulation necrosis surrounded by fibrosis and some area of hemorrhage. In two cases, ce-MRI showed the presence of residual enhancing tissue on 3D GRE T1-weighted images and pathology confirmed the presence of viable tumor cells. This failure was attributed to device malfunction in one case and to patient motion in the other case. In 2/10 cases, we found no enhancing tissue on ce-MRI, while pathology revealed a small focus of apparently viable cells located in the middle of the ablated area and surrounded by necrotic cells. In this case, it could be possible that we caused heat fixation of the cells, preserving their morphological aspects but completely eliminating their functionality [51]. Anyway, electronic microscopy should be mandatory to confirm such hypothesis. In all cases, no tumoral cells were found in resected lymph nodes. After the surgery, all patients underwent radiotherapy and, if possible, hormonal therapy. At 6 months follow-up, no evidence of local recurrence was seen in all cases at imaging.

## Expert commentary

HIFU is already established as a valid noninvasive technique for ablation of benign and malignant tumors in various organs. Even if surgery remains the gold standard for the treatment of breast lesions, HIFU has a strong potential role for the ablation of benign and malignant breast neoplasms in order to provide a valid noninvasive alternative treatment for breast conserving surgery.

With regard to benign breast lesions (fibroadenomas), USg-FUS has proven very useful for young patients who refuse surgery or want to avoid surgical scar or are not candidates for conventional surgery for medical reasons; its use is often required also in young patients with multiple and/or bilateral nodules of medium-to-large dimensions or in patients with fibroadenomas causing discomfort because of the position or the dimension. The use of US guidance instead of MR makes this method cheaper, simpler and more comfortable for the patient. Compared to the other mini-invasive techniques, USg-FUS is less invasive despite its longer duration.

Regarding malignant breast neoplasms, from our experience, we can state with good confidence that women are strongly interested in this noninvasive technology, thanks to its noninvasiveness and to the possibility of performing treatments using just a mild conscious sedation, also with a totally uncomplicated postoperative course. The small number of treated patients must be certainly counted as a study limitation affecting the statistical power of the study. Anyway, the literature reports similar results in different countries. Sheng Li reported results obtained in different studies performed between 2002 and 2010 in 173 patients treated with US or MR HIFU. In 123 patients, a complete ablation rate of 71% was found [52].

The US guidance surely represents a useful tool in order to avoid long duration of the procedure, for claustrophobic patients or in the presence of MR-noncompatible materials. Moreover, better efficacy was reported in literature for patients treated under US guidance. Anyway, these results may be related to many factors, including differences in patient selection and operator's experience.

From the other point of view, contrast-enhanced MRI has been shown to be more precise and reproducible than US in determining lesion location, size, number and borders of breast cancer. These characteristics ensure better safety and efficacy for the patient. Moreover, even though there are difficulties in cases of fatty breasts, the assessment of the temperature increase within the focal point during sonication is better achieved with dedicated MR sequences rather than US.

With both techniques, some limitations still remain, with particular regard to the duration of the procedure, which remains very long and can lead to discomfort with the position and consequent incomplete ablation due to patient movement.

## Five-year view

With the recent FDA and CE approval of HIFU technique for the treatment of various organs, the scientific interest for the use of this technology is progressively increasing in several fields of research. In the field of breast pathology, the use of this technique has collected a particular interest, mostly due to its non-invasive and conservative approach. Moreover, the technical advances in diagnostic imaging have increased the early diagnosis and the consequent treatment of very small breast lesions.

Either under MR or US guidance, the results obtained until now are very promising (5-year disease-free survival of 95% published by Wu *et al.* [15]). Moreover, several studies are currently ongoing and are expected to be in clinical use in the near future.

The present study provided the exclusive treatment of invasive ductal carcinoma; the main limitation in treating lobular invasive carcinoma is represented by the fact that this type of neoplasm may have a substantially increased propensity for multifocal and multicentric distribution and bilaterality. Nevertheless, there are some studies published in literature that reported the ablation of different histotype of breast cancer such as lobular carcinoma or adenocarcinoma with variable results.

Different studies are also promoting research in a more technical field, in order to improve the equipment available [53,54]. Over the next 5 years, progressive improvement in technical devices will exponentially increase the number of patients undergoing HIFU treatments; thus, the larger number of collected data will provide a deeper knowledge of the mechanisms that underlie this technology. Moreover, randomized multicentric studies must be carried out in order to understand the true potential role of this technique.

### Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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## Key issues

- High-intensity focused ultrasound (HIFU) is a valid noninvasive technique that ensures tissue ablation in various organs. The use of an extra-corporeal transducer makes this technique less invasive compared to other percutaneous procedures.
- The ultrasound guidance allows the capability to treat breast fibroadenomas during free breathing of the patient. Moreover, it allows performing the treatment with the patient standing in a comfortable position.
- Even if ultrasound-guided HIFU was performed without the use of contrast agent, the changes in the echogenicity ensured the presence of thermal damage and consequent coagulation necrosis inside the nodule.
- Preliminary results obtained at 3 months after HIFU treatment demonstrate a 50% reduction of the maximum diameter of the treated fibroadenomas.
- Magnetic resonance guidance represents an added value in order to better visualize the margins and the dimensions of the area to be treated, allowing an accurate planning of the procedure.
- The use of dedicated sequences allows having a real-time monitoring of the temperature increase within breast target tissue. Moreover, the capability to have a real-time temperature monitoring increases the safety of the procedure, avoiding thermal damage to the surrounding anatomical structures.
- The use of Gd-enhanced sequences allows having a quick assessment of the treatment efficacy, immediately at the end of the procedure.
- Results obtained in patients with invasive ductal carcinoma of the breast show the absence of residual neoplastic cells in 60% of treated cases.

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