Review

Magnetic resonance image-guided versus ultrasound-guided high-intensity focused ultrasound in the treatment of breast cancer

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Abstract

Image-guided high-intensity focused ultrasound (HIFU) has been used for more than ten years, primarily in the treatment of liver and prostate cancers. HIFU has the advantages of precise cancer ablation and excellent protection of healthy tissue. Breast cancer is a common cancer in women. HIFU therapy, in combination with other therapies, has the potential to improve both oncologic and cosmetic outcomes for breast cancer patients by providing a curative therapy that conserves mammary shape. Currently, HIFU therapy is not commonly used in breast cancer treatment, and efforts to promote the application of HIFU is expected. In this article, we compare different image-guided models for HIFU and reviewed the status, drawbacks, and potential of HIFU therapy for breast cancer.

Key words High-intensity focused ultrasound, breast cancer, magnetic resonance imaging, ultrasound, ablation

High-intensity focused ultrasound (HIFU) is a type of non-invasive, local ablation therapy in which external ultrasonic energy is transmitted into a lesion using an extracorporeal approach, leading to coagulative necrosis of the tumor. Hence, targeted lesions are completely destroyed *in situ*, leaving the skin intact.

Ultrasound (US)- or magnetic resonance image (MRI)–guided HIFU therapy has been used to ablate localized solid tumors[1,2]. In the United States and European countries, MRI-guided HIFU is used mainly to treat prostate cancer and uterine fibroids, whereas in China, US-guided HIFU therapy is used to treat hepatocellular carcinoma and other solid tumors[3]. Each image-guided method has advantages and disadvantages.

Breast cancer is a common malignancy. With the improvement of medical science and technology, non-invasive or mini-invasive therapies have become increasingly common. Compared with other techniques, HIFU is an ideal breast-conserving therapy because HIFU does not significantly change the patient's mammary shape and does not cause bleeding or scarring after the procedure. Additionally, HIFU can preserve the structure and function of the breast postoperatively with excellent cosmetic results. HIFU therapy can also maintain skin integrity and may play an important role in breast-conserving cancer therapies in the future. We compare US-guided and MRI-guided HIFU and summarize the current status and main problems with using HIFU therapy for breast cancer to date.

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Magnetic Resonance Image-guided and Ultrasound-guided High-intensity Focused Ultrasound

US and MRI are the main guidance modalities for HIFU therapy. Each of them has unique merits (**Table 1**). A basic diagram depicting HIFU therapy is shown in **Figure 1**.

Procedural planning

Preoperatively, the use of MRI provides high spatial resolution in an arbitrary plane. MRI enables an accurate assessment of the extent of tumor infiltration and stage as well as the critical surrounding structures. In breast cancer, MRI can be used to obtain 3-dimensional (3D), anatomic, and high-resolution images that clearly illustrate the relationship between the tumor and surrounding tissues or organs. This information helps reduce the risk of damaging organs and other structures, including the heart, ribs, and peripheral nerves. As a result, MRI is an invaluable tool for planning the most precise ablation trajectory for a focused US beam. Comparatively, US generates lower

Table 1. The comparison of magnetic resonance imaging (MRI) and ultrasound

Parameter	MRI	Ultrasound
Real-time	Quasi real-time	Real-time
Resolution	Good	Affected by many factors
Blinking spot	No	Yes
Thermometry	Able	Unable
Grayscale change	Visible	Invisible
Image quality	Providing clear images, larger field-of-view	Combination with other imaging modalities needed
Efficacy evaluation	Done immediately after the procedure	Delayed assessment
Artifacts	Less	Obvious
Cost	Expensive	Cheap
Compatibility	Not compatible for some devices	Compatible
Sound shadow	Without shadow	Obvious shadow
Three-dimension structure	Multiple planar imaging	3D ultrasound
The stability of image quality	Excellent correlation with pathologic results	Manipulator variability, it may become worse during the procedure

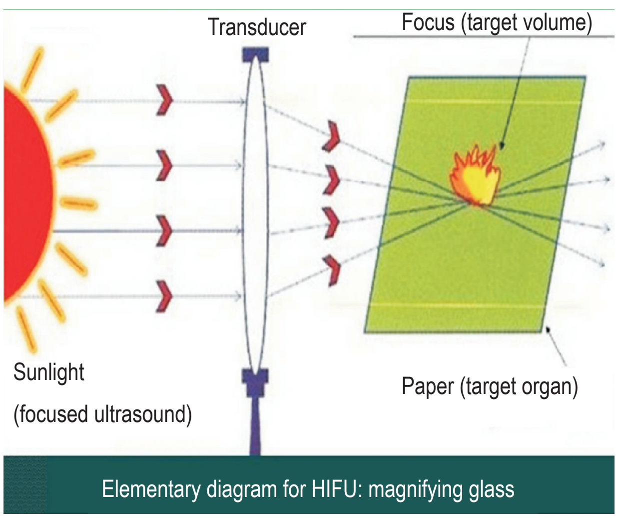

Figure 1. **Basic diagram depicting high-intensity focused ultrasound (HIFU) therapy**

quality spatial resolution but better visualization of a single lesion and tumor borders. Thus, US is also a useful tool for determining the exact borders and precise location of masses for ablation.

Both MRI- and US-guided techniques can be used to measure the distance between the skin and the superficial or deep surface of the tumor, regardless of whether the involved skin and chest wall areas can be directly imaged. However, MRI has been shown to be more precise and reproducible than US in determining the exact location and extent of breast cancer in a given patient, as well as the amount of intraductal spread. The improvement of 3T MRI from the previous 1.5T MRI further increases the ability of MRI to define tumor borders.

MRI allows a larger scanning range and provides more reliable images than US. MRI can be used to identify ipsilateral axillary, supraclavicular, and parasternal lymph nodes positive for lesions with less user variability than US[4,5]. In breast cancer, the lesion location, size, number, and borders are more clearly visualized using MRI. MRI recognizes isoechoic lesions that are not apparent using US imaging. Thus, MRI is important in locating the full extent of lesions in both breasts. Overall, MRI is a more comprehensive and thorough method for locating lesions.

Real-time 3D US provides 3D structural images[6]. This imaging modality can precisely determine the gross target volume and borders of normal tissue, providing protection for surrounding vital organs and achieving complete ablation of the tumor at the same time. However, MRI offers excellent 3D images at a higher spatial resolution and more quickly than 3D US in most situations.

MRI is not appropriate for patients with magnetic metal implants. The resulting artifacts influence the quality of imaging, and more importantly, implants may endanger patients during HIFU therapy.

US-guided HIFU does not have this contraindication.

Image fusion combines the advantages of both imaging modalities. Through the process of image registration, different imaging data from the same field can be transformed onto a one-coordinate system. In terms of real-time imaging, the integration of US with either CT [7,8] or MRI [9,10] retains the merits of US and avoids drawbacks such as fog artifacts. US and MR fusion imaging combined with a navigation system combines the strengths and eliminates the shortcomings of the two modalities. Integrated images are useful for visualizing isoechoic lesions, small lesions, and lesions shielded by artifacts, gas, or the bones. Thus, image fusion is useful for identifying the precise position of the tumor. However, image fusion requires further study to address registration errors due to breast displacement.

Intra-procedural targeting

MRI provides excellent soft tissue differentiation and spatial resolution. Using 3D imaging, the exact location of the tumor and its relationship to the surrounding tissues or organs can be easily identified, all of which lead to improved treatment. The MRI-guided procedure is not affected by bubbles or artifacts produced during the procedure, which is an important problem with US-guided HIFU. For example, artifacts in superficial regions affect the visualization of tumors in deeper regions. The quality of US imaging is affected by the ultrasonic frequency, the tumor location, the state of the skin, and the manipulator's experience[11]. Furthermore, there are two additional disadvantages to US-guided therapy: the presence of a blind area and the identification of isoechoic lesions, which are difficult to view using US imaging. Combining US with other imaging modalities may overcome these specific problems.

With breast MR images, all lesions are fully displayed, and imaging lesions in arbitrary planes aids in the identification of the best ablation trajectory. US alone can also be used for this purpose, but with limited image definition. MRI can identify more breast lesions overall, although contrast-enhanced US often shows additional lesions less robustly. The extent of cancerous tissue is more accurately imaged using MRI than US.

Quasi real-time MRI is not beneficial for the treatment of tumors located near the skin or ribs because the procedure can damage these tissues. Furthermore, breast deformation due to breathing or irregular displacement may affect the treatment of breast cancers with HIFU[12]. However, target lesions can be tracked during breathing or deformation of the breast with US, which has the attributes of collecting images in real time and easy operation.

Because MRI guidance is sensitive to temperature, the focal spot can be identified with the MR thermometry technique[13,14]. Thus, the operator can quickly determine the precision of the ablation in 3D space and obtain accurate information about tumor borders and the organs at risk, greatly improving the accuracy of ablation and avoiding damage to critical normal structures. Therefore, this guidance model can increase efficacy and reduce complications. MRI-guided HIFU can also be used to aid the ablation of non-palpable breast lesions. The ribs, gas, scars, subcutaneous fat, and calcified tissue produce acoustic shadows and affect the quality of US-imaged lesions, leading to reduced image resolution and the possible shielding of lesions. There are also some regions in the body that are blind to US. Furthermore, the power to identify deep tissue lesions is decreased compared to MRI because of diagnostic US attenuation. Thus, accurate determination of the location of lesions and efficacy of evaluation are impaired when using US only.

During HIFU therapy, the identification of lesions and the risk to important organs can be affected due to swelling of the skin, skeletal reflection, necrotic lesions in the near path of the US beam, and the appearance of mist-like artifacts. All of these factors impair the effectiveness of clinical monitoring, lesion identification, and operation with US guidance. On the other hand, MRI-guided HIFU works well under these circumstances.

Monitoring

Real-time imaging

US guidance is useful, providing real-time imaging at a relatively low cost, although with a limited field of view, spatial resolution, and contrast resolution.

Using real-time US monitoring, treatment effects can be assessed by immediate grayscale changes. By examining this feedback, operators can control the thermal dose delivered. If there are obvious grayscale changes and a sufficient cumulative energy deposition, coagulative necrosis always occurs [15, 16]. Increasing the ultrasonic grayscale level in the target volume is generally considered a signal of effective treatment and is caused by coagulative necrosis of the target lesions, cavitation bubbles, and other unidentified factors. By examining the appearance of the hyper-echoic area, complete necrosis can be assessed and breast skin burn can also be identified. After ablation, with an increased grayscale level and the appearance of a rear acoustic shadow, it is not always easy to observe remaining active lesions or the focal point.

Because of tissue edema, increasing acoustic attenuation and the heterogeneity of lesions, some lesions with coagulative necrosis do not show apparent grayscale changes, despite confirmation of necrosis by pathologic examination. At the same time, increased grayscale changes do not always mean complete necrosis of the cancerous lesion[9,10].

Currently, MRI is the only available technique that provides quantitative temperature measurements. MRI can facilitate temperature monitoring and diagnosis, which is more objective in terms of necrotic assessment. When the temperature rises to a certain level, coagulative necrosis or normal tissue damage occurs. Compared to US, MRI provides a very clear anatomic image but is still too slow to provide real-time anatomic images for temperature measurements.

However, if the thermometry zone moves, it is difficult to measure the temperature changes during an HIFU procedure. This limits the application of MRI-guided HIFU. As a result, keeping patients immobile is critical during the procedure. This problem is less pronounced during US-guided HIFU. Clinical practice and research have shown that US can effectively monitor the treatment response (coagulative necrosis) using grayscale changes or contrast-enhanced US.

High-speed magnetic resonance imaging

MRI is suboptimal for real-time monitoring compared to US due to its relatively slow imaging speed. Breast displacement will occur during ablation, and current MRI machinery does not operate fast enough for true real-time monitoring. It is likely that this problem will be solved in the future. During the procedure, HIFU operators should ensure a safe treatment borders around the lesion to prevent damage to adjacent organs. MRI is still not fast enough to accurately image breast displacement and therefore cannot thoroughly ablate breast cancer and protect nearby organs.

With the technical improvements to high-speed MRI, the goal of real-time visualization for the HIFU procedure has been achieved on a basic level. Currently, the fast MRI sequences include fast spin echo sequence, gradient echo sequence, and echo planar imaging sequence. Fast spin echo imaging sequences can be completed within a few seconds and, in abdominal imaging, can exclude artifacts induced by respiratory motion. However, this sequence still does not meet the real-time monitoring requirements for HIFU. The echo planar imaging sequence (EPI) is a very fast imaging method, acquiring 10 to 20 images per second depending on the subtype of sequence used. This technique meets the needs of fast monitoring and efficacy evaluation in HIFU therapy.

Non-invasive temperature monitoring

MRI is extremely sensitive to temperature changes and is especially suitable for the display and control of thermal energy deposits[17]. MRI is able to measure temperatures *in vivo* with excellent sensitivity. T1- and T2-weighted signal changes are also observed during breast MRI with increasing temperature. The extent of ablation and any damage to normal tissue can be determined on the basis of the *in vivo* temperature reached. This can help the operator accurately control the ablation temperature, protect surrounding structures, and predict the extent of the ablated volume by ensuring that the thermal exposure is sufficient within the target volume and that the appropriate dose is delivered near critical structures. At present, there are 3 temperature-sensitive parameters for MRI. When the molecular diffusion coefficient (diffusion coefficient) is used for thermometry, it often takes 2 to 3 min to obtain an image, which is too slow for real-time monitoring. Two other parameters are commonly used, including proton resonance frequency shift (PRFS) and longitudinal relaxation time (T1). With US imaging, the focal spot still cannot be visualized, and the temperature elevations cannot be precisely measured.

Proton resonance frequency shift

Changes to the hydrogen PRFS have a linear relationship with temperature changes; therefore, temperature changes are reflected by hydrogen PRFS changes. During the procedure, MRI can accurately monitor energy deposition. Thermometry based primarily on PRFS[13,14] is a reliable method for the quantification of temperature changes *in vivo*, which can provide active feedback on the thermal exposure in lesions. Chen *et al.*[13] concluded that PRFS-weighted imaging was sensitive to temperature changes and could display the focal spot directly in the magnitude images.

The most common problem for PRFS-based thermometry is the sensitivity of image collection to motion. Promising methods have been proposed in recent years [18], combining PRFS imaging alternately with water apparent diffusion coefficient (ADC) imaging to generate thermal images that are corrected for drift. This technique is applicable to the correction of sudden, large, motion-related discontinuities in PRFS imaging. Echo planar [19] and gradient-echo [20] imaging techniques have also been tested for temperature imaging.

Longitudinal relaxation time (T1)

The value of T1 is sensitive to temperature changes, and the rise in temperature will cause a longer T1 signal. MR thermometry is very accurate, monitoring as little as a 1°C change in still tissue. Even if thermometry is affected by breathing or heartbeat, temperature changes of 2°C to 3°C can be monitored. When using the US inversion method with thermometry during HIFU, and the thermometry accuracy in animal experiments was approximately ± 3°C[14]. Therefore, MR thermometry can monitor temperature changes in the targeted tissue during HIFU therapy for efficacy evaluation. If the temperature in the targeted tissue is above 65°C, the lesion has been considered to undergo coagulative necrosis. The identification of methods to accurately monitor temperature changes during the procedure remains a pressing problem for MRI-guided HIFU therapy, which requires real-time thermometry of the tumor borders at a minimum resolution of 1 cm.

Magnetic resonance and ultrasonic elastography

Magnetic resonance elastography (MRE) [21, 22] is a rapidly developing technique to quantitatively assess the mechanical stiffness of tissue by examining the propagation of mechanical waves through the tissue with a special MR technique. Although this technique is expensive, each direction of particle displacement can be accurately measured within the tissue on the nano level, and the need for precise quantification of elastic coefficients can be achieved. MRE is being investigated for application to breast diseases. A potential application of MRE is the differential diagnosis of breast cancer [23, 24]; results from previous studies demonstrated an easily observable separation between breast cancer and fibroadenoma when using the shear modulus. Typically, breast cancers are known to be stiffer than benign lesions and normal breast tissue [25].

Contrast-enhanced MRI has a very high sensitivity for the detection of tumor nodules but is limited by the specificity of this technique [26]. A combination of MRE and contrast-enhanced MRI shows promise for increasing the diagnostic specificity for breast diseases [27]. It is likely that MRE can help achieve imaging palpation. Wu *et al.* [28] concluded that MRE technology could reflect changes in the organizational tissue structure so that the solidification of target breast tissue after HIFU therapy could be evaluated. The mechanical characteristics of ablated tissue and normal tissue around the tumor are vastly different, and these differences can be imaged and quantified using MRE. These conclusions were confirmed in bovine muscle tissue ablated during *in vivo* experiments, which also demonstrated a new method for the evaluation of tissue solidification after HIFU therapy. When there is coagulative necrosis in the target region, tissue elasticity also changes. Le *et al.* [29] performed MRE within target tissues during HIFU therapy and found that because changes in the elasticity of the target tissue occur, data for therapeutic evaluation can be obtained.

Ultrasound elastography (USE) can also be used to monitor changes in tumor hardness during HIFU therapy [30-33]. The first and most common application of elastography is the differential diagnosis of benign and malignant breast lesions [34-36]. This method has the lowest cost/efficiency ratio and provides complementary information that increases the diagnostic specificity of US [37, 38]. The drawback is that variability and image quality between operators may influence overall performance with USE. Obviously, MRE is less affected by observer variability. Previous studies have confirmed that coagulative necrosis in tissue can be identified and that the lesion borders and size can be reliably visualized with axial-shear strain elastography during HIFU therapy. These results demonstrated the potential of quasi real-time guidance and monitoring during HIFU therapy. Tissue damage caused by HIFU can be effectively detected by USE [39], improving the ability to precisely control the extent of ablation.

Overall, both MRE and USE can be used to determine a differential diagnosis of benign or malignant breast lesions and to monitor HIFU therapy, although observer variability and image quality is a potential drawback of USE.

Motion artifact and compatibility problems

Fast imaging technologies and other techniques can solve the problem of motion artifacts [40, 41] involved in breast MR scanning. Patients with implanted stents or instruments made of ferromagnetic material, such as pacemakers, are not suitable for MRI-guided therapy because of safety and imaging quality concerns. However, this situation provides another application for US-guided HIFU. When MRI-guided therapy is used, surgical auxiliary equipments, such as anesthesia-monitoring equipments [42] and ablation devices, require magnetic compatibility and the ability to function well in a strong magnetic field without significant interference from artifacts. As a result, spatial configuration and electromagnetic shielding for these devices must be considered. Currently, compatible surgical equipments and surgical navigation products are available.

Both guidance modalities lack ionizing radiation. The main disadvantages of MRI-guided HIFU include the need to use magnetically compatible devices, a relatively high cost, motion artifacts, and obvious noise for patients, whereas US is relatively inexpensive and quiet for patients and does not require equipments with magnetic compatibility.

Controls

US is used for the real-time tracking of breast lesions so that the ablation time and power can be promptly adjusted according to intra-operative changes. Patients are requested to remain in a certain position to maintain spatially fixed breast lesions during the HIFU procedure. If a large displacement appears, MRI-guided HIFU is often not fast enough to respond to these changes. Using a 1.0 Tesla open MRI-guided ablation system, 7 pictures can be obtained in 1 s during the procedure, fulfilling the real-time imaging requirement.

MR thermal imaging is useful to verify the focal zone and monitor increases in temperature to ensure that a sufficient and exact thermal dose is delivered. With US imaging, the focal spot cannot be localized as precisely as with MRI. Very often, necrosis is judged by grayscale changes with US-guided HIFU [15, 16]. Even so, the focal spot and coagulative necrosis can be effectively judged using US imaging. Wu's studies [43-45] demonstrated that effective and safe HIFU therapy of breast cancer could also be obtained using US guidance. High-frequency diagnostic US is sensitive enough to detect exact breast cancer margins, which aids in the complete destruction of breast tumors.

Postoperative evaluations

Both contrast-enhanced MRI and US can visualize the blood supply of the tumor and be used to evaluate complete necrosis after the HIFU procedure. Tissue coagulation can be detected using either contrast-enhanced MRI or US immediately after the procedure, but with different sensitivities and specificities.

Dynamic contrast-enhanced MRI is more objective and reliable for the accurate assessment of ablation results because it uses signal changes and observable defects in the blood flow supplied to ablated lesions. The presence of residual cancerous lesions or positive ablation margins can be determined with MRI and long-term follow-up after the procedure. In contrast, grayscale changes in US imaging, colored blood-flow signals, and dynamic contrast-enhanced US are markers for the immediate evaluation of coagulative necrosis of cancerous lesions.

Contrast-enhanced US imaging with encapsulated dye poly-lactic-co-glycolic acid (PLGA) micro-bubbles or nano-bubbles[46-48] has the potential to be a valuable tool for intra-operative assessment of tumor borders and therapeutic margins[49]. These biodegradable multifunctional active agents, which play a dual role in diagnosis and treatment[50], can provide contrast-enhanced imaging before the procedure, enhance cavitation[51] and ablation effects during the procedure, and contribute to understanding the filling defect in the ablation area postoperatively.

Contrast-enhanced MRI offers advantages such as ensuring that the exact coagulation extent can be visualized and that the entire tumor can be completely destroyed during HIFU therapy; thus, ablation is guaranteed in one treatment cycle. The treated area will present as non-enhancing foci after contrast administration [52]. Using diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps, the treated or untreated tissue shows different ADC values [52]. Hazle *et al.* [53] reported that the region without enhancement could lead to an underestimation of the extent of tissue necrosis after treatment, which was verified histologically.

In conclusion, MRI-guided HIFU may represent the future direction of image-guided, minimally invasive therapy. Although US is inexpensive, can acquire real-time images, and is convenient, it has blind spots and is operator dependent (**Table 1**). Image fusion may provide the best combination of the two modalities discussed above.

The Status of High-intensity Focused Ultrasound Therapy for Breast Cancer

The efficacy of HIFU therapy for breast cancer

The benefits of HIFU therapy for breast cancer include the following: no bleeding, preserving the structure and function of breast tissue, no scarring, and little change to breast shape. Breast cancer surgery often requires complete hemostasis to avoid complications. When considering the merits of HIFU therapy, the prevention of bleeding-related complications is important. HIFU therapy is also highly repeatable and does not have radiation.

However, it is not easy to obtain complete pathologic specimens, pathologic classification, and TNM staging after HIFU ablation. Hence, whether there are residual microscopic lesions near ablation margins is unknown.

To achieve the same results as a total mastectomy, HIFU ablation of breast cancer should achieve complete (100%) tumor necrosis. Histopathologic analysis indicated that the complete necrosis rate of breast cancers treated with HIFU ablation in recent years is between 20% and 100% [54-62]. Specifically, Wu *et al.* [43-45] reported 100% tumor necrosis in all patients treated with US-guided HIFU therapy, with pathologic confirmation. However, the ablation rate of breast cancer treated with MRI-guided HIFU was 20% to 95% [54-62]. These differing results may be associated with a number of factors, including differences in patient selection, the image-guided technique used, the equipment used, and the operator's experience. However, the key factor may be ablation margin.

During the period 2002-2010, multiple international clinical studies on HIFU ablation to treat breast cancer were conducted. Within the 11 arms of breast cancer treatment guided by US or MRI, there were a total of 173 patients treated with HIFU therapy, and tumor diameters were 0.5 cm to 6.0 cm (Table 2). Some patients underwent adjuvant chemotherapy, endocrine treatment, and/or axillary lymph node dissection. After ablation, patients underwent resection, multiple-point biopsy, or long-term follow-up. Malignant tumors in 123 patients were completely necrotic, with a complete ablation rate of 71% (123/173), which was confirmed by pathologic examination or long-term follow-up. The complete necrosis rate of breast cancer treated by MRI-guided HIFU was 59% (71/121), whereas the complete necrosis rate of breast cancer treated by US-guided HIFU was 96% (50/52). It appears that the patients treated by MRI-guided HIFU did not have better outcomes than patients treated by US-guided HIFU. Meanwhile, the cosmetic results of most patients with breast cancer under both guidance modalities were excellent. HIFU has great potential for the non-invasive treatment of breast cancer. The authors concluded that HIFU ablation was safe and effective for breast cancer treatment. However, these studies were small; large, prospective, randomized studies are needed to further investigate the efficacy of HIFU therapy.

Complications

Skin burn may be the most common complication from HIFU (**Table 2**). Overall, 8 cases of skin burn were reported in the MRI-guided HIFU group, whereas only 1 case was reported in the US-guided HIFU group. However, 11 cases in the US-guided HIFU group required short-term oral analgesics, and 6 cases with mammary edema and injury to the pectoralis major muscle were reported. Reflection at the soft tissue-bone interface may result in transient temperature increases [63] and thermal damage to healthy tissues. Rib tissue in the HIFU post-focal region can easily absorb energy, leading to rib pain after the procedure using either image-guided modality. Zderic *et al.* [64] believe that bubble formation at the HIFU focus might provide a way to shield the post-focal region from unwanted thermal effects. Therefore, bubble formation is a potential solution and may prevent some damage. Short-term pain might be common, and some patients will require oral analgesics for several days.

The rates of complete breast cancer ablation ranged from 0 to 100% after treatment with one of the following minimally invasive therapies: radiofrequency ablation, laser ablation, microwave ablation, or cryoablation, with 3% to 8% of patients reporting skin burn in most studies. Muscle burn, pneumothorax, and skin ulceration and necrosis were also mentioned in a few studies [65].

Three major problems with high-intensity focused ultrasound therapy for breast cancer

Some uncertainties exist using HIFU ablation to treat breast cancer; thus, important indications can be gained from previous studies of conservative breast therapies involving surgery and radiation.

The ablation margin

It is important to know the appropriate ablation margin because it is related to local recurrence and long-term survival. The amount of healthy breast tissue that should be destroyed and how to increase the probability of complete tumor necrosis in HIFU procedures are two issues under investigation. Studies of breast-conserving surgery can provide important information. Although breast-conserving surgery is the standard treatment, positive resection margins can still be identified in 10% to 53% of patients [66, 67]. Therefore, the extent of tumor infiltration must first be fully understood.

Necessity of a negative margin for breast-conserving surgery

Six large, prospective, randomized studies were designed to study breast-conserving surgery: Milan I, IGR [68], NSABP-B06 [69], NCI, EORTC, and DBCG [70]. With more than 4,000 cases, the total survival rates in two arms of the study (breast-conserving therapy with whole breast radiotherapy compared to mastectomy) were not significantly different, indicating that survival for most breast cancer patients is not dependent on the choice of mastectomy or breast-conserving therapy. During more than 15 years of follow-up, these studies revealed that the local recurrence rate of patients who

Table 2. Overview of studies on high-intensity focused ultrasound ablation for breast cancer

Study	No of tumors	Pathology	Tumor size	Complete ablation	Cosmetic results	Complications	Image guidance
Huber *et al.* (2001) [55]	1	Invasive ductal carcinoma	2.2 cm	Surgical resection in the treated part of the tumor, cells were partly necrotic and mostly sublethally damaged	Good	The skin over the treated area did not exhibit any ultrasound-related visible changes	MRI
Gianfelice *et al.* (2003) [56]	12	Invasive ductal carcinoma (*n*=10), invasive lobular carcinoma (*n*=1), adenocarcinoma (*n*=1)	All tumors <3.5 cm	Routine segmental tumor resection, complete necrosis (33%, 4/12)		Minor skin burns (16.6%, 2/12), tenderness around the treatment zone (25%, 3/12)	MRI
Gianfelice *et al.* (2003) [57]	17	Invasive ductal carcinoma (*n* = 14), adenocarcinoma (*n* = 2), invasive lobular carcinoma (*n* = 1)	< 3.5 cm	Complete necrosis (23%, 4/17), residual cancer volume below 10% (53%, 9/17); residual cancer volume between 30% and 75% (23%, 4/17)	None mentioned; routine segmental resection	None mentioned	MRI
Gianfelice *et al.* (2003)[61]	24	Biopsy–proven breast carcinoma	All tumors < 3.5 cm	Surgical resection, complete necrosis (79%, 19/24)	Not mentioned	Two degree skin burn (4%, 1/24)	MRI
Zippel *et al.* (2005)[58]	10	Infiltrating breast carcinoma	All tumors < 3 cm	Surgical resection; complete necrosis (20%, 2/10). Microscopic foci of residual tumor (20%, 2/10); 10% residual tumor (30%, 3/10) and 10%–30% residual tumor (30%, 3/10)	Acceptable cosmetic results (10%, 1/10)	No infection; two degree skin burn (20%, 2/10)	MRI
Khiat *et al.*(2006)[59]	26	Invasive ductal carcinoma (*n*=25), infiltrating lobular carcinoma (*n*=1)	< 3.5 cm	Surgical resection; complete necrosis (28%, 7/26); less than 10% residual tumor (42%, 11/26)	No reports	No reports	MRI
Furusawa *et al.* (2006)[60]	30	Invasive ductal carcinoma (*n*=25), invasive mucinous adenocarcinoma (*n*=1), DCIS (*n*=2), intraductal carcinoma(*n*=1), noninvasive ductal carcinoma (*n*=1)	All tumors < 3 cm	Mean necrosis rate of breast tumors 96.9%. Complete necrosis (50%,15/30) Between 95% to 100% necrosis (36%,12/30)	A reliable replacement for lumpectomy	Three degree skin burn (3%, 1/30); One required treatment termination due to pain, abdominal and breast skin redness (3%, 1/30)	MRI
Furusawa *et al.*(2007)[62]	21	Invasive or noninvasive ductal carcinoma	0.5 to 5 cm	Mean follow-up 14 months; complete necrosis (95%, 20/21); one recurrence (5%)	Dimple on the skin (4.5%, 1/21)	Skin burns (9%, 2/21)	MRI
Wu *et al.* (2003) [43]	23	Invasive breast cancer (*n*=21)	< 6 cm	Surgical resection; complete necrosis (100%, 23/23)	No changes of mammary shape	Minimal skin burn (3%, 1/23); 5 patients needed oral analgesics	Ultrasound
Wu *et al.* (2005) [45]	23	Invasive breast cancer (*n*=21), noninvasive breast cancer (*n* =1)	All tumors < 5 cm	No surgical resection; 100% complete necrosis (100%, 23/23); local recurrence (9%, 2/23) after 18 and 22 months, respectively	Good to excellent in 94%, acceptable in 6%	Six patients needed oral analgesics (18%, 6/23). No skin burn, bleeding, or infection	Ultrasound
Kim *et al.* (2010)[54]	6	Invasive ductal carcinoma	1.2 to 3.7 cm	Surgical resection and biopsy; complete necrosis (66%, 4/6)	Skin thickening and trabecular thickening	Mammary edema and injury to the pectoralis major muscle (100%, 6/6), disappearing 6 months later.	Ultrasound
Total 2001–2007	173			20%–100%	Excellent in most patients	skin burn at least (4.5%, 8/176)	

underwent breast-conserving surgery in three trials was much higher than that of patients who underwent mastectomy: 8.8% vs. 2.3% in the Milan I trial [71], 22% vs. 0% in the NCI trial [72], and 20% vs. 12% in the EORTC trial [73, 74]. The two groups in the NCI trial and the EORTC trial enrolled patients with positive margins. After 40 years of studying breast-conserving treatments, it should once again be emphasized that negative margins are the basis for local control of lesions.

Radiotherapy for breast-conserving therapy: negative or positive margins

Radiotherapy can reduce the local recurrence of breast cancer with negative or positive margins and is necessary for breast-conserving therapy. Six small studies [75-80], with a total of 153 cases, found that the local recurrence rate in the vicinity of the primary lesion was 83%, demonstrating that the majority of recurrences were in the vicinity of the tumor bed [81]. Pathologic studies also demonstrated that for most patients, the majority of foci in the breast were quite close to the primary lesion [82]. This suggests that postoperative radiotherapy exerts its maximal effect by eradicating residual foci near the tumor bed for the local control of lesions. Therefore, HIFU therapy for breast conservation must be combined with radiotherapy. After HIFU breast-conserving therapy, the necessity of a boost for the tumor bed has been discussed. In the EORTC 22881-10882 trial conducted by Bartelink *et al.*[83], local recurrence was reported as ranking first in treatment failure in 278 patients with no boost compared to 165 patients with a boost; the cumulative incidence of local recurrence was 10.2% versus 6.2% for the two groups at 10 years, respectively ($P < 0.001$). The 10-year survival rate was 82% in both arms. The authors concluded that a boost dose of 16 Gy led to improved local control of lesions in the boost group, but no benefits in improving overall survival.

High-intensity focused ultrasound ablation volume in breast cancer

It is difficult to confirm whether the margin is negative after HIFU therapy for breast cancer, and generating a sufficient tumor-free margin is a challenge. Wu *et al.* [44] reported that the range of HIFU ablation for breast cancer was 1.5 to 2 cm and the complete necrosis rate was 100%. Kearney *et al.* [84] examined a group of 239 cases of breast-conserving surgery. If 0.5 to 1.0 cm of normal tissue around the tumor was excised, 95% of patients had negative margins. Veronesi *et al.* [71] reported that in 43% of 282 patients, foci were found more than 2 cm beyond the edge of the reference tumor. To conserve breast tissue, HIFU therapy should rely on surgical excision data to determine the area for ablation.

Efficacy evaluation: correlation of breast magnetic resonance imaging with histopathology

Precise knowledge about the prevalence of these occult disease components at various distances to the MRI-visible lesion is essential when HIFU is planned or guided on the basis of MRI.

Schmitz *et al.*[85] examined 62 patients (64 breasts) who underwent an MR scan and breast-conserving therapy and were prospectively included in the study to compare MRI findings with histopathology. The mean size difference between the MRI-visible lesion and the index tumor was 1.3 mm. Subclinical disease occurred in 52% and 25% of the specimens at distances ⩾ 10 mm and ⩾ 20 mm, respectively, from the MRI-visible lesion. Schmitz *et al.* concluded that typical treatment margins of 10 mm around the MRI-visible lesion might include occult disease in 52% of patients. When surgery achieves a 20 mm tumor-free margin around the MRI-visible lesion, 25% patients should also be treated with radiotherapy.

Multifocal or multicentric breast cancer

Multifocal or multicentric breast cancer is defined as the presence of two or more cancerous foci around the main malignant mass within one or multiple quadrants of the same breast, respectively. Invasive multifocal or multicentric breast cancer in patients with clinically and/or radiologically unifocal lesions is an important problem for ablation therapy because it is difficult to identify and destroy these clinically and/or radiologically negative lesions during HIFU therapy. Relevant data can be found in total mastectomy cases. Fisher *et al.* [86] observed multicentric non-invasive cancers in 10% of the patients treated by total mastectomy and believed that 86% of local recurrences following lumpectomy occurred within or close to the same quadrant as the index cancer. Veronesi *et al.* [71] found that in 282 patients with multifocal or multicentric invasive breast cancer with clinically and/or radiologically unifocal tumors, 264 had tumors smaller than 4 cm in diameter. In 56 (20%) patients, tumor foci were present within 2 cm of the main lesion, and in 121 (43%) patients, tumors were beyond 2 cm from the index tumor. In 46 lesions (16%), the tumor foci beyond 2 cm were histologically invasive cancers. The authors estimated that the expected local recurrence after breast-conserving surgery was related to the extent of the excision. From the above two studies, it is estimated that patients with foci beyond 2 cm from the index lesion account for approximately 4.3% of patients with breast cancer.

Because of its non-invasiveness, pathologically negative margins cannot easily be ensured after HIFU therapy, and the margin status often must be assessed by imaging. Negative margins seen with imaging do not always represent pathologically negative margins, and a pathologically negative margin is not always equal to the absence of malignant tissue in multifocal or multicentric breast cancer. For these reasons, radiotherapy is a necessary part of treatment.

Is breast-conserving therapy with HIFU potentially feasible for multifocal or multicentric breast cancer? Studies have been conducted examining breast-conserving surgery in patients with multifocal or multicentric breast cancer and reported a high risk of local recurrence. In fact, Kurtz *et al.*[87] examined 61 patients with multiple macroscopic tumor nodules, and concluded that the local recurrence rate was 36% in patients with invasive breast cancer. Wilson *et al.* [88] observed that the local recurrence rate was 25% in 13 patients with multiple breast cancers. Recently, some investigators [89-92] have reported that in selected cases, the combination of breast-conserving surgery with radiation resulted in a 2% to 5% locoregional recurrence rate. Harris *et al.* [81] and Gentilini *et al.* [93] were strongly in favor of breast-conserving surgery combined with radiotherapy in selected patients with multifocal or multicentric breast cancer, provided that the treatment was technically and cosmetically feasible, in their retrospective studies separately examining 476 and 147 patients. After combining breast-conserving therapy with radiotherapy, a 5-year survival rate and low local recurrence for patients with multifocal or multicentric breast cancer undergoing breast-conserving therapy was observed in some cases [94].

Mass problem after radiotherapy for breast–conserving therapy

After HIFU therapy for breast cancer, surgical resection has also been performed for further pathologic study, and residual lesions are sometimes found, suggesting that postoperative radiotherapy is necessary to reduce the local recurrence of tumors. However, peripheral capillaries are easily occluded after radiotherapy. Therefore, after ablation, it may take much longer for the lesion to be fully absorbed and dissipated [45]. If the mass continues to be in the breast, or even if an abscess forms within the mass, it causes an additional psychologic burden to the patient. To the best of our knowledge, there are no published reports describing solutions to this problem.

In summary, US is inexpensive and convenient and can be performed in real-time, whereas MRI can attain high-resolution images and provide thermometry data. Image fusion may be the next important modality for real-time and effective guidance in breast cancers treated with HIFU. Several studies with different necrotic rates have shown HIFU to be effective and safe for breast cancer treatment. The complete necrosis rate observed is higher using US-guided HIFU with fewer cases of skin burn. There are three problems requiring careful consideration with HIFU therapy: the ablation margin, the presence of multiple breast cancers, and necrotic masses remaining in the breast after treatment.

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