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INTERVENTIONAL RADIOLOGY

REVIEW

Magnetic resonance imaging-guided radiofrequency ablation of breast cancer: a current state of the art review

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ABSTRACT

With a gradual increase in breast cancer incidence and mortality rates and an urgent need to improve patient prognosis and cosmetology, magnetic resonance imaging (MRI)-guided radiofrequency ablation (RFA) therapy has attracted wide attention as a new treatment method for breast cancer. MRI-RFA results in a higher complete ablation rate and extremely low recurrence and complication rates. Thus, it may be used as an independent treatment for breast cancer or adjuvant to breast-conserving surgery to reduce the extent of breast resection. Furthermore, with MRI guidance, accurate control of RFA can be achieved, and breast cancer treatment can enter a new stage of minimally invasive, safe, and comprehensive therapy. With progress in MR thermometry technology, the applications of MRI are expected to broaden.

KEYWORDS

MRI-guided, breast cancer, radiofrequency ablation, interventional therapy, MR thermometry

According to Global Cancer Statistics 2020, breast cancer has replaced lung cancer as the most common cancer diagnosed in women globally.[1] It is estimated that, within 10 years, new cases of breast cancer will rise worldwide to 2,300,000, and deaths due to breast cancer will rise to 684,996, increases of 35.3% and 30.7%, respectively.[2] Changes in reproductive patterns that are associated with an increased breast cancer risk, such as delays in childbearing and fewer births, may have contributed to this historic increase.[3] The proportion of younger patients (<49 years old) has likewise increased over the years. As economies grow and beauty standards change, patients with breast cancer who seek treatment will have higher standards for their quality of life, aesthetics, and social and psychological recovery that surgery may fail to meet due to its proclivity for more extensive damage to the appearance of the breast and troublesome complications.

Accordingly, minimally invasive and non-invasive operations, such as radiofrequency ablation (RFA), microwave ablation (MWA), laser ablation (LA), high-intensity focused ultrasound (HIFU), and cryoablation, have been increasingly favored as treatments for breast cancer.[4] Among these methods, magnetic resonance imaging-guided RFA (MRI-RFA) has become one of the major modalities used in minimally invasive breast cancer treatment,[5] as it optimizes cosmetic results with shorter operative times and fewer complications. However, there is currently no review article regarding MRI-RFA. This article describes the current applications and development of this therapy to provide a reference for the clinical treatment and research of breast cancer.

1. Current status and progress of MRI in the clinical diagnosis and treatment of breast cancer

MRI has been used as a supplementary diagnostic tool for the general survey of breast cancer over the last 100 years, especially in those who fail to receive precise diagnoses by X-ray or ultrasound (US), those who are staging or planning breast-conserving surgery (BCS) before

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operation, those who require an evaluation of axillary lymph node metastasis, and those at high genetic risk.[6] With advantages such as non-ionizing radiation, multiplane and multiparameter imaging, and high soft-tissue resolution, MRI has a level of examination efficiency that X-ray and computed tomography (CT) do not share and that leads to fewer missed diagnoses of malignant nodules in class 4 of the Breast Imaging Reporting and Data System.[7]

MRI performs exceptionally in the identification of occult breast cancers, carcinomas *in situ*, multifocal carcinomas, ductal infiltrating carcinomas, and intraductal papillomas. In a correlation study, Lee et al.[8] found that, in 26% of 38 cases, the presumed sonographic correlate was not the true correlate, as a subsequent MRI-guided biopsy of the actual lesion revealed one malignancy among discordant cases. This is in line with the results of another meta-analysis suggesting that MRI has greater sensitivity than US in detecting nodal metastases.[9]

Besides its use in diagnosis, dynamic contrast-enhanced (DCE) MRI, the most sensitive modality of breast imaging, now plays a crucial role in interventional therapeutic regimens for breast cancer.[10] It offers imaging guidance for tumor localization with the ability to evaluate and adjust probe placement during the operation. Moreover, it performs better than mammography, CT, and US in identifying information about tumor boundary and blood supply.[11] In the minimally invasive treatment of breast cancer under imaging guidance, it has been used frequently[12-15] to monitor the presence of postoperative residual tumor, fibrous scarring, steatonecrosis, and tumor recurrence after radiotherapy[16] and neoadjuvant surgery.[17]

Main points

- This review seeks to summarize the current therapeutic principles, adaptations, and procedures of magnetic resonance imaging-guided radiofrequency ablation (MRI-RFA) of breast cancer to encourage further exploration of this program.
- MRI-RFA's role in treating diseases such as breast cancer has been profound, and due to its imaging advantages, it excels in accurately targeting lesions. It is also useful for monitoring recurrence.
- MR thermometry allows practitioners to monitor temperature changes in real time to minimize injury to patients and evaluate the ablation process during the procedure.

2. Treatment principles and technical advantages of MRI-RFA

2.1. Principles of RFA for tumor treatment

Once the radiofrequency ablation needle penetration into the tumor through the skin under the guidance of an image is achieved, frequency waves are emitted through the needle tip. These frequency waves will lead to the movement of ions and particles in tissues causing collision and friction, leading to the generation of biological heat effect.[18] During RFA treatment, the temperature of the probe needle tip reaches as high as 70°C–120°C. Due to poor heat dissipation of the tumor tissue, high temperature can cause degeneration, dissolution, coagulative necrosis and even carbonization of cancer cells. The blood within the tumor vessels also undergoes coagulation, so that the heat will not dissipate with the blood flow, thermal damage is limited to a precise range.[19] Furthermore, the possibility for tumor metastasis with blood flow can be also declined.

In addition, RFA can coagulate the vascular tissue around the tumor and form a reaction zone about 0.5 ~ 1 cm thick, separating the tumor from the surrounding normal tissue, which can not only block the blood supply of malignant tumors, but also prevent distant metastasis to a certain extent.[20]

2.2. Technical advantages of MRI-RFA: ablation method

With the popularization of minimally invasive treatments for tumors, the clinical value of ablation technologies, such as RFA, MWA, LA, HIFU, and cryoablation, has improved substantially. According to a meta-analysis of 1.608 cases by Peek et al.[21], when comparing all ablative treatment options, RFA appears to perform optimally.[22,23] In terms of its shorter treatment time (compared with HIFU), fewer short-term complications (compared with LA), and extremely low tumor recurrence rate among all methods, MRI-RFA presents certain advantages above other ablation methods.

Nonetheless, there exist some virtues of other ablation methods that RFA does not possess. Compared with RFA, HIFU leaves no scars. MRI-HIFU is now applied in uterine fibroids and bone metastasis-related pain management with a Comformité Européenne (CE) mark and United States Food and Drug Administration approval.[14,15,24] Additionally, compared with RFA, the treatment procedure for cryoablation is less painful and more comfortable, though it carries the risk of an incomplete ablation of perivascular lesions with a rich blood supply, as shown by Morin et al.[25] and Pusztaszeri et al.[26]

In recent years, the use of MWA in clinical trials of early-stage breast cancer[27] has revealed that it can act as the trigger of an antitumor immune response in the Th1 variety of inducible T-cell co-stimulator (ICOS) pathways.[28] Thus, targeted agents based on MWA-induced systemic immune responses have aroused broad interest. Although it can accomplish a larger ablation volume within a short period, it is not clear if MWA offers more value than RFA,[29,30] and operational difficulties and high costs related to equipment maintenance could also be a hindrance.

2.3. Technical advantages of MRI-RFA: imaging technique

On this basis of MRI-RFA technique, new treatment methods have been proposed and practiced. After confirming the presence of the malignant nodules of early micro- or occult lesions with MRI-guided biopsy, RFA can be employed as an accurate, minimally invasive, and efficient treatment. In addition, the complete ablation rate and boundary of tumor tissue that has been completely inactivated can be evaluated through the real-time measurement of physiological parameters during MRI[31] [e.g., by proton resonance frequency (PRF), spin lattice relaxation time, and apparent dispersion coefficient (ADC)].

With the parameter and imaging advantages mentioned above, RFA can provide opportunities for reducing the degree of thermal damage to normal tissue under artificial control. The PRF shift (PRFS) has crystallized as the method of choice for temperature measurement due to its linear variability with temperature in most tissues, with the exception of fat, which contains relatively few hydrogen bonds and a small PRF thermal coefficient compared with water.

In recent years, there have been many efforts to confront the application restrictions of MR thermometry in areas with high fat content, such as the breasts and abdomen. Cheng et al.[32] proposed a dual-step iterative temperature estimation of a fat-referenced PRFS method to improve both the accuracy and precision of temperature estimations in fat-containing tissues. T1- and T2-based[33] methods have been implemented recently to correct thermometry errors brought on by the non-local effects of heating in fatty tissues[34] or as an adjunct to PRFS thermometry in aqueous tissues (glandular, tumor, etc.).[35]

In addition, multi-echo MR thermometry using iterative water–fat separation techniques[36] has been validated in simulations, phantom heating experiments, and *in vivo* breast and liver experiments. This method could help monitor ablative therapies in fatty tissues[34] such as the breast or liver. In contrast, US guidance cannot quantify the heat deposited in ablation target tissue.[37] Moreover, the shadow and strong echo generated by breast tissue when heated can affect the evaluation of any curative effect, making it more difficult to guarantee the completeness of any real-time monitoring of ablation by US.[18,38,39]

3. Application of MRI-RFA in breast cancer therapy

MRI entered the clinical study of RFA for breast cancer for the first time when van den Bosch et al.[40] pioneered the use of 0.5T MRI for the RFA treatment of breast cancer, providing a new path for patients with advanced invasive breast cancer. Based on previous studies,[32,41,42] the MRI-RFA procedure is summarized as follows: 1) patient lies in a prone position with the breast fixed on a biopsy frame with a breast coil; 2) appropriate puncture path is determined and puncture point is marked; 3) surgical drape is placed, surgical field is disinfected, and local anesthesia is administered; 4) the needle tip is verified to exceed the tumor edge by 0.5–1.0 cm; 5) RFA power is gradually adjusted to about 50 W to maintain a temperature of 100°C for 5–10 minutes, and a 0.9% NaCl aqueous solution at 0°–5°C is injected into the system in continuous circulation to maintain the uniform energy distribution of the needle tip; 6) ablation range changes, blood supply, and the ADC of the ablation area are monitored by MRI (the residual tumor will be monitored during timely supplementary treatment); and 7) regular follow-up after operation is required. The summarized procedure is depicted in Figure 1.

A personalized, comprehensive treatment approach for advanced breast cancer has been gradually gaining ground, and MRI-RFA has caught clinicians' and patients' eyes as a preferred treatment method. Here, the indications and contraindications of MRI-RFA for breast cancer are summarized, as shown in Table 1.

Neoadjuvant therapy makes it possible to downstage breast cancer and shrink tumors, giving access to BCS to patients who were initially ineligible.[43] Moreover, for those who are not candidates for surgery, MRI-RFA, which is expected to completely eliminate local tumors, can be offered as an alternative.[44]

Currently, axillary staging after neoadjuvant systemic therapy has contributed greatly to decreasing the incidence of axillary lymph node dissection (ALND) and its concomitant morbidities (especially lymphedema). While sentinel lymph node biopsy (SLNB) may be less valuable in MRI-RFA than in surgery as an independent treatment for local lesions, the value of SLNB after RFA warrants discussion to guide further systemic therapies, including endocrine, chemical, and targeted therapies.

Additionally, when there are positive sentinel node, radiotherapy has proved to have good curative effect of local lesion in axilla, which is comparable to that of ALND but with less morbidity and pain.[45] Notably, there are concerns about whether SLNB should be offered to older people and those with underlying medical conditions. Although it is less invasive than ALND, a patient's condition should always be considered comprehensively.[46]

3.1. Application of MRI-RFA in the treatment of small breast cancer

So far, MRI-RFA has only been put into clinical practice to treat small-diameter tumors in patients with moderately advanced breast cancer. In 2008, van den Bosch et al.[40] performed the first clinical study of MRI-RFA in patients with advanced invasive ductal carcinoma (1.2–2.3 cm in diameter). Three patients achieved 100%, 50%, and 33% tumor tissue ablation effects, respectively. In 2017, Yunian et al.[42] administered RFA treatment to 11 patients with breast cancer with persistent residual tumors (1.5–3 cm) post-med-

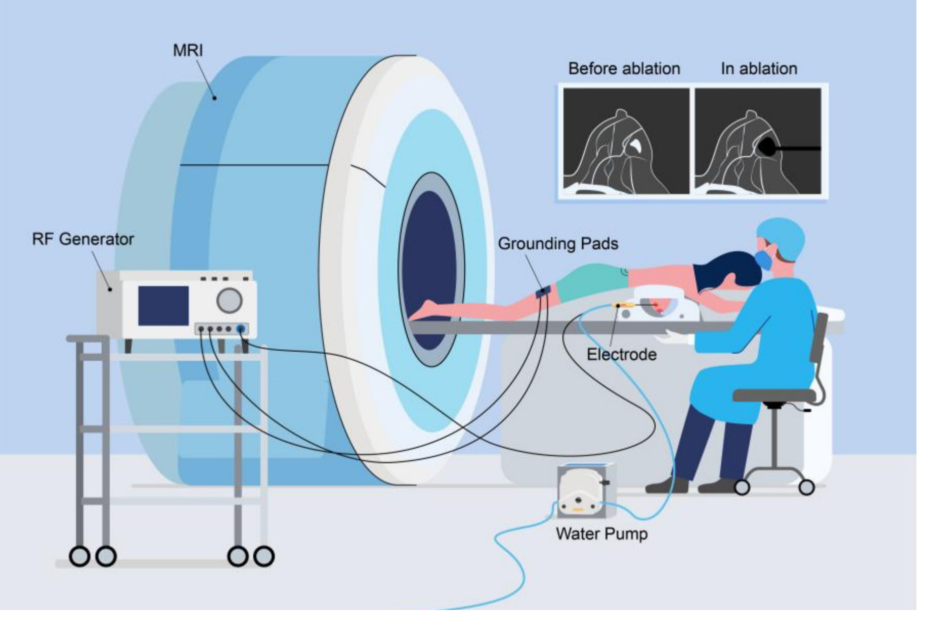

Figure 1. Procedure for magnetic resonance imaging radiofrequency ablation therapy for breast cancer. Patient lies prone with the breast placed on the biopsy frame with breast coil. The radiofrequency generator provides the necessary ablation energy which is applied through the needle into the tumor tissue. The water pump is utilized to adjust and maintain the temperature of the needle tip. MRI, magnetic resonance imaging.

Table 1. Indications and contraindications for MRI-RFA treatment of breast cancer

	Indications	Contraindications
Tumor characteristics	Tumor diameter <3 cm	Extensive or diffuse lesions
	Tumor margin >1 cm from the chest wall/skin	Malignant characteristic calcifications of diffuse distribution.
Combined factors	Severe underlying disease	Inflammatory breast cancer
	Tumor remains after non-surgical resection and multidisciplinary treatment	Severe coagulopathy, cardiovascular, and cerebrovascular diseases and those who cannot tolerate surgery
	Wishes of patients and their families	Pacemaker implantation and claustrophobia during MRI examination

MRI-RFA, magnetic resonance imaging-guided radiofrequency ablation.

ication therapy. Li et al.[41] implemented MRI-RFA in 10 patients with moderately advanced breast cancer (tumors ≤3 cm in diameter). After at least one ablation, all cases achieved a radiographically complete response with a low complication rate and mild symptoms, and there were no recurrences or metastases at 2 years' follow-up. All of these studies confirm the safety and efficacy of MRI-RFA.

A comparison of these studies reveals that van den Bosch et al.[40] adopted a multi-needle RF system (in claw/umbrella shape) with an open 0.5T scanning imager in their study, while the others chose a cool-tip needle RF system with a 1.5T scanning imager. The multi-needle system used in the first study can better conform to more extensive lesions and simultaneously show the temperature distribution of the warming tissues via the FluorOptic fiber optic thermal sensor of its probe tip (Figure 2). At the same time, the MRI-compatible cryoprobes used in the other studies make it possible for circulated cooling of the RF needle tip. Furthermore, for corrections of susceptibility arteacts from MRI-compatible cryoprobes, van den Bosch et al.[40] recommend specific pulse sequences, such as view angle tilting, which helps mitigate distortion.

DCE-MRI was utilized for needle tip placement in all of the above studies to accurately identify the characteristics and boundaries of lesions. In addition, van den Bosch et al.[40] selected T1-fast spin echo (FSE) for imaging accurate probe placement and fewer artifacts, while PRFS thermometry (without reference) is used for the quantitative mapping of temperatures throughout the procedure. The other two studies also added the application of diffusion-weighted imaging (DWI) sequences into their procedures. There are increasing developments in the usage of ADC that add value to the diagnosis[47] and localization of breast cancer[48,49] and breast DWI as an essential part of a multiparametric breast MRI is welcome by the European Society of Breast Radiology.[50] Dietzel et al.[51] found that DWI can be used as a substitute for the delayed phase in DCE-MRI, shortening the scanning time without losing diagnostic information.

Tumor size also plays a role in the control of injury and treatment effect. Xia et al.[52] found that, as far as achieving a complete response, RFA performs better in treating breast cancer tumors with a diameter of <2 cm than those <3 cm in diameter. Ohtani et al.[53] found that a single RFA treatment can eradicate breast cancer of less than 1.5 cm in diameter without ductal invasion, while tumors larger than 1.5 cm in diameter may require two or more RFA treatments. Thus, to effectively exploit the advantages of MRI-RFA in the treatment of small breast tumors, further experiments are needed to determine the most suitable tumor diameter and biomorphological characteristics for this treatment.

3.2. Application of MRI-RFA in conservative surgery for breast cancer

Studies have shown that negative tumor margins can reduce the rate of tumor recurrence to some extent, be effective for local tumor control, and achieve better tumor-free margins compared to tumor resection.[54,55] Moreover, MRI-RFA may be an effective procedure to avoid reoperation after tumor resection. However, excessive resection of breast tissue make its contour and aesthetic challenging to maintain. Reducing the residual lesion within the tumor bed through BCS is the key to reducing its recurrence. In some retrospective analyses, RFA treatment in neoadjuvant post-BCS led to a lower recurrence rate and higher cosmetic outcome satisfaction score than in neoadjuvant post-BCS alone. Zhang et al.[56] demonstrated the reliability and value of MRI-RFA's clinical application with an extremely low recurrence rate (0.87%) and low complication rate (3.48%).

The potential for the clinical implementation of RFA for treating breast cancer largely depends on the accuracy of the imaging techniques employed to assess tumor extent and guide ablation.[21,57] and MRI has shown high accuracy in detecting residual disease after RFA in patients with invasive breast cancer. It is conceivable that inactivating viable residual tumor cells at tumor-resection margins with MRI-RFA makes it possible to effectively reduce the extent of glandular tissue resection in BCS, which guarantees better preservation of the patient's breast contour. MRI-RFA treatment of free margins may lead breast-conserving therapy into a new stage. However, large sample multicenter studies, prospective clinical trials, and long-term follow-ups need to be implemented to support the validity of this study.

3.3. Evaluation of the efficacy of MRI-RFA in breast cancer treatment

It has been shown that MRI can significantly increase the detection rates of breast cancer remnants and recurrence depending on the shape of lesions, discrepancy of signal, enhancement characteristics, and dynamic time–signal curve. A tumor activity analysis of residual lesions on postoperative MRIs can be marked by distortion and alterations of signal intensity in the ablation zone. Mild enhancement can be detected at the margin of lesions, and MRI findings after ablation may be correlated with their histological results,[57,58] which is beneficial to the prediction and monitoring of tumor metastasis in patients after operation.

As noted earlier, as a crucial part of multiparameter imaging based on DCE-MRI, DWI is applied not only in the diagnosis and localization of breast cancer but also in the evaluation of ablation efficacy. After the procedure, MRI showed that the structure of the ablation area was disordered, the edge of the lesion was slightly enhanced, or its periphery was scattered with irregular enhancement. Nodular or eccentric enhancement could be observed in follow-up. Burak et al.[59] observed that imaging manifestations of residual tumors were correlated with a discrepancy in contrast enhancement, a finding verified by

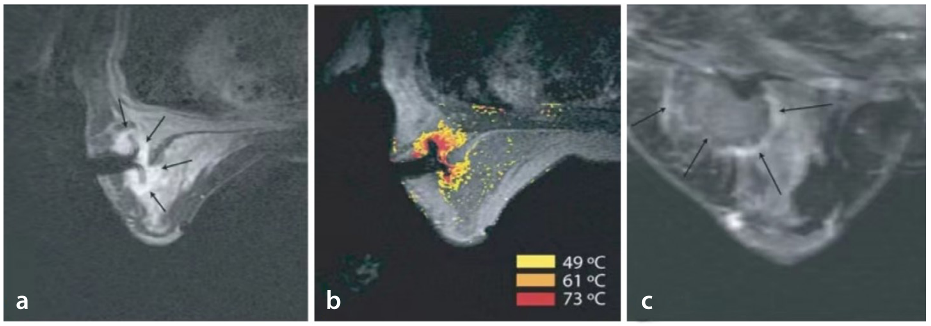

Figure 2. (a) Axial Comformité Européenne (CE) three-point Dixon gradient-echo images of the first patient in prone position showing the enhancing tumor mass (arrow) lateral in the right breast with the hypointense fully deployed LeVeen needle electrode centrally in the mass. **(b)** Axial CE three-point Dixon gradient-echo images of the same patient in prone position showing the magnetic resonance proton resonance frequency shift thermo map (yellow zone: 49°C, orange: 61°C, red: 73°C) around the hypointense deployed LeVeen needle electrode centrally in the mass (arrow). **(c)** Post-procedure CE water-selective, spectral-spatial axial FSE image of the right breast demonstrates a small enhancing rim representing the border of the ablation zone corresponding to fresh scar tissue (arrows) (van den Bosch et al.[40], 2008).

van den Bosch et al.[40], Li et al.[41], and Yunian et al.[42], who used maximum intensity projection (MIP) images to monitor tumors. They found that tumor blood supply disappeared in 100% of MIP images, and the ADC value of DWI was higher than before ablation, indicating complete ablation. In contrast, a lower ADC value after operation[40,41] suggested that residual tumor remained, and supplementary RFA therapy should be considered.

Yamamoto et al.[60] performed a subsequent prospective MRI evaluation of small breast cancers treated with RFA prior to radiotherapy and chemotherapy and found that tumor margins could be determined to some extent. The probe placement during surgery and ablation completeness could also be predicted by MRI. The studies above indicate that MRI is necessary for evaluating post-ablation surgery, allowing prompt evaluation of possible tumor residuals, providing a basis for timely supplementary ablation, and demonstrating ablation's high safety and efficacy. However, this study is limited to a single center with a small number of cases. Further multicenter studies with large samples and prospective cohort studies are needed to offer a positive confirmation of MRI's clinical value.

3.4. Complications of MRI-RFA in breast cancer treatment

Due to patients' physical differences, complications after MRI-RFA treatment of breast cancer are diffuse and specific, but most can be predicted and controlled. The most common complication is burning of the skin, characterized by skin redness, elevated skin temperature at the body surface projection area of the lesion, and in severe cases, blisters. When the tumor is close to the chest wall, the skin is less than 1 cm thick, or multiple ablations are required to achieve satisfactory results, it is recommended to take specific protective measures, such as using a cool-tip needle for ablation during operation[39] or placing a sterile ice bag on the skin surface of the tumor. When skin temperature rises, cold saline gauze can be applied locally, and cold saline or 5% glucose solution can be injected subcutaneously to form a peritumoral isolation zone. Postoperative temperature measurement and care of the tumor area can involve the intermittent use of an ice compress[61] to reduce potential skin damage. Burning pain in the operative area can often be relieved by local injection of lidocaine[62] or by regional nerve block anesthesia before the operation begins.

Complications such as nipple discharge, burns, or retractions are rare. Yamamoto et al.[60] reported a rare case of chronic postoperative granulomatous mastitis in the surgical area, which they posited was related to an excessive autoimmune reaction induced by fat extravasation and production of this fluid after ablation. Therefore, comprehensive and predictable evaluations must be conducted prior to and after clinical treatment to develop an individualized therapeutic plan according to the size, location, and degree of enhancement of the patient's lesions. However, MRI can make a difference in reducing intraoperative pain in patients, preventing skin damage, and minimizing complications.

Conclusion

To conclude, MRI-RFA is a safe, feasible, minimally invasive, and less-painful interventional oncological procedure, rivalling surgical or other percutaneous techniques in its effectiveness as a partial treatment for' early breast cancer. Due to its advantages in radiation, visualization, and real-time evaluation, MRI-RFA is being gradually accepted by clinicians and patients alike as a potentially valuable modality in treating breast cancer. To reduce the extent of extended resection and preserve breast integrity while ensuring negative margins, the introduction of MRI-RFA during BCS deserves more intensive investigation for patients with breast tumors of larger diameter. In addition, there is an urgent need to further explore the extraction of tumor characteristics related to the efficacy of MRI-RFA and to carry out more comparative efficacy evaluations and experimental studies focused on other means of ablation therapy to set reasonable and standardized indications and contraindications and thus maximize the benefit to patients. Further studies are also needed based on SLNB pro-RFA to guide management of the axilla. Toward this end, multicenter longitudinal studies and explorations of MRI-RFA in combination with systemic therapy require more attention.

Although technical issues, such as cost and MRI-RFA's compatibility with interventional equipment, impose constraints on its clinical application, MRI has assumed a supportive role in prompting medicine to evolve from precision diagnostics toward refined therapeutics. It is the key to improving the physiological and psychological prognoses of patients. With the development of technology and economic progression, the clinical application of MRI-RFA will gradually be generalized. Whether the effect of comprehensive treatment is similar to or better than that of traditional BCS requires further study. As such, collecting more empirical data to guide MRI-RFA's standardized application and help improve and innovate core technologies (e.g., ablation implementation and temperature monitoring) will offer a new treatment path for doctors and patients.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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