Image-Guided Ablation in Breast Cancer Treatment

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In the past 2 decades, new and improved imaging technologies and the use of breast cancer screening have led to the detection of smaller and earlier-stage breast cancers. Furthermore, there has been a trend toward less aggressive treatment of small breast cancers, which has led to the development of less invasive alternatives than surgery with promising effectiveness, and less morbidity. Many patients are not satisfied with the cosmetic outcome after breast-conservation therapy. Better cosmesis can be achieved with less invasive techniques. Moreover, less aggressive treatment options would be very useful in patients older than 70 years with comorbidities that make surgery a difficult and sometimes life-threatening treatment. Minimally invasive ablation techniques have been studied in early-stage small tumors with the goal of attaining efficacy similar to that of breast-conservation therapy. These techniques would have less scarring and pain, lower costs, better preservation of breast tissue, superior cosmesis, and faster recovery time. Breast lesions can be destroyed by thermal methods, that is, by heating or freezing the tissue. There are 5 types of thermal ablations that have been or currently are in research clinical trials: cryoablation, radiofrequency, laser, microwave, and high-intensity focused ultrasound ablation. The first 4 methods destroy cancers using percutaneous image-guided probe placement. High-intensity focused ultrasound is noninvasive, performed without any skin opening.

Tech Vasc Interventional Rad 17:49-54 © 2014 Elsevier Inc. All rights reserved.

KEYWORDS Cryoablation, Radiofrequency Ablation, Breast Cancer, High Intensity focused Ultrasound ablation, Minimally Invasive Ablation

Overview

Pretreatment imaging with mammography, ultrasound, and magnetic resonance imaging (MRI) to accurately define the extent and volume of tumor is important for appropriate patient selection. Size and location of the tumor from the skin, the heart, and the pectoralis muscle are necessary to select appropriate tumors and to plan the approach. Patients with an extensive intraductal tumor or invasive lobular carcinoma should be excluded if the goal is complete tumor ablation. Before ablations, core needle biopsy should obtain all necessary histologic information regarding receptors. Sentinel lymph node status should be determined, as lymph drainage may be disturbed after ablation. Postablation MRI is useful to define complete tumor necrosis. Ablations needing ultrasound or MRI guidance for targeting ideally should be performed by physicians who are experienced at targeting breast lesions with image-guided needle biopsies.

All ablation methods vary in technical advantages and disadvantages and stages of development for clinical use. These techniques are investigational, and their accuracy and optimal methods of performance are still evolving.

Cryoablation

Cryoablation has been the subject of numerous national and international clinical trials for the treatment of breast cancer, with accuracy varying from 36%-93%. The greatest success in complete cell death has occurred in tumors <2 cm in diameter, and especially those that are 1.5 cm or smaller, without extensive ductal carcinoma in situ. Patients with tumors >2 cm are generally considered poor candidates owing to the presence of
sonographically occult tumor extension. Cryoablation has been used as a final treatment for large and higher-stage tumors among elderly patients with nonresectable breast cancer or patients refusing surgery, with no recurrence reported at 18 months.5,6

Cryoablation for the treatment of small breast cancers has been reported in phase I and II trials, with removal of the ablated tumor within 1-4 weeks after the ablation and histopathologic review for presence of residual tumor.4 Among more recent studies, MRI has been employed for pretreatment evaluation to identify patients with tumor extension beyond that visible on ultrasound. Posttreatment MRI identifies patients who have residual disease. Among 15 patients who had MRI examinations after cryoablation, an MRI cryohalo was found, indicating cryoablation efficacy and clear margins.7 The most recent cryoablation clinical trial among 15 women with lesions 4-12 mm in diameter reported that MRI was accurate in detecting the solitary case of 3-mm residual tumor, considered owing to suboptimal eccentric probe positioning during cryoablation.1

Cell death is achieved by freezing tissue with a percutaneous 3-mm probe, typically with ultrasound guidance (Fig. 1A and B).8 Freezing causes cell death owing to extracellular and intracellular ice formation, altered tissue osmosis, cell membrane damage, and lysis. Freezing also damages the vessels feeding the tumor, leading to anoxia. Two freeze-thaw cycles of approximately <10 minutes each are used, which results in more effective tissue necrosis than 1 cycle. The total procedure time is approximately 30-40 minutes with the patient supine in comfortable position. The freezing (<40°C to −160°C) is accomplished by rapid argon gas expansion (Joule-Thompson effect) or by liquid nitrogen, generating an ice ball of 4-7 cm, monitored by ultrasound (Fig. 1C). The ice ball has a discrete hyperechoic rim, depicting the border between frozen and unfrozen tissues. At least a 1-cm thick margin of ice beyond the tumor surface is necessary to assure complete cell death. During freezing, saline is injected between the ice ball and the skin to prevent skin damage that may occur if the ice ball rim is <5 mm of the skin (Fig. 2). The saline injections enable safe treatment of cancers that are close to the skin, unlike heat-based ablations (Fig. 3).9,10 Thawing of the ice ball is passive or actively done using helium gas expansion, which enables removal of the probe from the ice ball.

Local anesthesia with lidocaine is the only analgesia necessary, as freezing is also analgesic. This is a significant advantage of cryoablation over heat-based ablations, which typically require general anesthesia or intravenous sedation. Reported complications are skin necrosis, which is caused by the ice ball being too close to the skin, and which is uncommon with experienced users. No complications to the chest wall or pectoralis muscle are reported. Over time, tissue necrosis and macrophage invasion occur, and if not resected, this tissue will be reabsorbed by the body. At surgical excision 2-4 weeks after cryoablation, a successful ablation demonstrates no viable tumor at histologic examination, only inflammatory cells and fat necrosis.9 Core biopsy to obtain sufficient samples before cryoablation and tumor destruction is important for identification of tumor type and receptors.11

Accurate probe insertion into the geometric center of the tumor is necessary to prevent positive margins. The tumor should be clearly depicted by ultrasound, and the operator should be highly experienced with ultrasound-guided procedures. Neither mammography nor ultrasound has been found to be completely accurate at prestaging the tumor (Fig. 4). Therefore, MRI, which is superior to ultrasound in determining local extent of a carcinoma,

**Figure 1** (A) Cryoablation probe is inserted into the mass (arrow). (B) Probe is inserted 1-1.5 cm beyond the mass (arrow). (C) When freezing begins, an ice ball forms around the probe, the ice ball appearing as a hypoechoic circumscribed mass (arrow).

**Figure 2** Transverse view of ice ball. Saline has been injected beneath the skin (arrow at hypoechogenicity), protecting the skin as enlarging ice ball rim approaches it.
has been more recently used to prestage tumors, and MRI guidance for cryoablation has also been described. However, the use of MRI during cryoablation is quite limited owing to logistical issues of working in an MRI suite and greater expense than ultrasound guidance.1,8

A limitation of cryoablation using ultrasound guidance is visibility of the tumor during the ablation, because the posterior tumor is obscured by extensive shadowing from the ice ball.9 Nonetheless, the location of the tumor can still be estimated within the ice ball. Cryoablation is not recommended for in situ disease or invasive lobular carcinoma, as it is difficult to determine precise extent of disease on ultrasound, and isolated foci may be missed.

Cryoablation of benign fibroadenomas is a Food and Drug Administration approved procedure that is available for routine clinical use. Complete disappearance of the fibroadenoma within a year is achieved in 95% of patients, with excellent cosmetic results and without significant complications.12 A multi-institutional study reported high patient satisfaction in community settings.13 Therefore, a useful model already exists for treating breast cancers with cryoablation using a commercial cryoablation system currently available. Cryoablation has also been described as a method for guiding surgical excision, similar to the wire localization technique. This eliminates the need for a procedure outside the operating room, and the frozen tissue may be easier to manipulate during surgical resection.14

Cryoablation is currently under investigation in the multicenter American College of Surgeons Oncology Group Z1072 clinical cryoablation trial.15 This clinical trial, the largest to date (100 patients, 20 clinical sites), is designed to determine if cryoablation can be successful in ablating stage 1 tumors, to study the efficacy of preablation MR in determining tumor extent, and postablation MR in measuring completeness of the ablation and the presence of residual tumor. MRI is performed 14-28 days after cryoablation, and a surgical lumpectomy is done 28 days after the MRI to evaluate for histologic residual tumor.

Antitumor immunity has been reported in animal models and patients after local thermoablative techniques.16 Tumor-specific immune responses stimulated by the damaged cells may contribute to control of metastases distant from the primary site,16 and in some instances, complete tumor regression has occurred.17 As opposed to the coagulative necrosis and massive protein denaturation seen with heat-based ablations, cryoablation allows for massive antigen presentation in the presence of proinflammatory cytokines. In animal models, improvements in the cytotoxicity of lymphocytes and of natural killer cell activation have been reported. Activation of natural killer cells in the presence of a tumor is significant, because natural killer cell activity is diminished by surgery. It is possible that a cryoimmunologic effect may be protective against tumor recurrence or distant metastases or both, either alone or in combination with adjuvant immunotherapies.10 Whether cryoablation stimulates an antitumor immune response that could alter recurrence or metastases is designed to be evaluated in the Z1072 clinical trial.

**Microwave Ablation**

Microwave ablation is a less commonly investigated method. It accomplishes heating by electromagnetic agitation of tissue water (dielectric heating) using frequencies...
between 900 MHz and 2450 MHz. This is less effective in low-water-content tissue such as adipose tissue. Thus, microwave thermotherapy may have a preferential heating effect on breast cancer cells compared with normal breast tissue, which has more fatty tissue. Two subtypes of this method with differing techniques and results have been reported: percutaneous microwave coagulation and focused microwave therapy. In focused microwave therapy, a probe is placed into the center of the tumor, usually with ultrasound guidance and the patient in a prone, breast-compressed position, similar to stereotactic core biopsy. This probe focuses the microwaves and monitors the microwave field amplitude during ablation. A fiber-optic temperature probe is also placed into the tumor to monitor therapy to the desired temperature, and additional temperature probes may be applied to the skin surface. A cooling system is used to decrease the risk of thermal injury to the skin. The duration of the procedure is approximately 60 minutes. With this method, the tumor necrosis is often heterogeneous, and early studies have indicated low success rates for complete ablation at 0%-8%. In a more recent clinical trial, this technique showed promise in reducing positive margins at excision and a statistically significant decrease in the size of tumors when combined with neoadjuvant chemotherapy. Complications of skin burns and severe pain were observed, and the prone position for a long duration causes more patient discomfort. A more recent study using percutaneous microwave coagulation obtained a 90% success rate among ≤3-cm breast cancers. This method is performed at 2450 MHz with a needle antenna placed into the center of the tumor. Poor position of the antenna and limited evaluation of tumor extent explained incomplete ablations. Continuous monitoring is done with ultrasound, and the tumor becomes echogenic and disappears within less than 10 minutes. Although this was a faster method and demonstrated greater feasibility for achieving complete ablation, the patients underwent general anesthesia, and thermal injury to pectoralis and skin burns were reported.

Focused Ultrasound Surgery

Ultrasound energy may be used for ablation using either interstitial applicators or extracorporeal transducers focused into the body. Focused ultrasound surgery (FUS) or high-intensity focused ultrasound (HIFU) is often used when describing extracorporeal ablation techniques. These systems tend to use air-backed transducers, or transducer arrays, for maximal power delivery into tissue. Transducers are acoustically coupled to the patient, and applied powers of 100 W operating at 1-2 MHz are used for highly conformal delivery of heat to a target within the breast. With current systems, the focal region is spatially limited, so multiple overlapping applications are necessary to ablate a larger target volume. Finding systems that can ablate larger lesions faster is an area of development. Generally, pretreatment imaging is used to both plan and target the lesion. Ultrasound imaging and MRI-guided focused ultrasound systems are currently being assessed. Although ultrasound has the benefit of being small, inexpensive, and relatively easy for guidance, MRI has the benefit of enhanced soft tissue contrast and the ability to visualize and quantify focal heating in the lesion. Monitoring of treatment progress is an area of research for both modalities.

MR-guided FUS systems typically use a modified MRI couch with an embedded transducer. The patient lies prone and is acoustically coupled to the system. Cooling of the tissue surface is often employed to prevent skin burns in the near field. Patients are usually anesthetized using intravenous conscious sedation. MRI is used to visualize the target region for planning, generally using contrast-enhanced T1-W images. Generally, care must be taken with lesion selection as lesions too close to the skin or chest wall can result in damage to these tissues from the increased power density proximal and distal to the beam focus. MR temperature imaging (MRTI) is employed to visualize heating during periods of sonication. Low-power test pulses can be used to periodically verify the location of the beam. Treatment is delivered under MRTI monitoring via using higher-power pulses (10-30 seconds) to ablate volumes (diameter of 1-5 mm and length of 0.5-3 cm) at the focus. The beam is moved mechanically and electronically to conformally deliver multiple sonications to the targeted tissue volume. Temperatures rise to 50°C-90°C in the focal region, with extremely sharp spatial gradients defining the region of damaged and undamaged tissue. There is a pause between sonications to allow tissue in the near field to cool back to baseline before the next pulse. Overall, this results in an extended treatment time of 45-120 minutes to cover a <2-cm diameter lesion.

Studies using FUS in breast are still scarce, with most studies being conducted as pilot feasibility and safety studies. Initial feasibility studies have resulted in variable complete ablation rates ranging from 24%-100%. In addition to the stated limits on lesion selection, additional concerns are the pain associated with the procedure as well as the ability for a consciously sedated patient to remain compliant in the prone position during the long procedure times. Analgesics may be directly injected to assist with the pain; however, there remain concerns about the safety of these materials in the FUS beam path and cavitation effects at the site of injection.

Radiofrequency Ablation

Radiofrequency ablation (RFA) is delivered via interstitial placement of a metal electrode into the breast. The electrode is attached to a radiofrequency generator generally operating in the range of 200 W at 400-800 kHz. The electrode induces current in the tissue adjacent to the electrode, and the heating of the tissue is because of resistive (Joule) heating via ionic agitation. As tissue is heated, conductivity is reduced, limiting the extent of ablation. A grounding pad placed on the skin is used to disperse the current density in the tissue away from the electrode. Additionally, active cooling of the electrode itself can be employed to aid in generating larger zones of ablation.
Ultrasound or MRI can be used to guide the placement of the electrode in the tissue using techniques similar to those used for image-guided biopsy. There are electrodes on the market that can be scanned in MRI under specific conditions. However, systems do not yet exist that enable simultaneous delivery of therapy while imaging in the MRI. Currently, the noise generated by the radiofrequency generator is prohibitive. For treatment delivery, the large electrode pad for grounding is often placed on the anterior thigh. This conductive pad is a potential site for MR-induced burns if left on the patient during MRI imaging. Using modern electrodes that have multiple tines, large ablation volumes (diameter of 3-6 cm) can be generated in reasonable times (10-15 minutes) with one placement. However, the treatment zone can be inhomogeneous because power deposition is a function of tissue conductivity, which changes during heating. Without imaging guidance, this makes control of the procedure and prediction of outcomes difficult.

For RFA techniques, initial feasibility studies range from 76%-100% complete ablation volumes. Multitine electrodes reportedly have difficulty deploying into hard, fibrous tissue. This, in conjunction with control over large volumes, may make the use of multiple single-tine electrodes to cover the target volume more attractive, although it can add to both expense and procedure time. As with other heat-based procedures, intraprocedural pain management is an issue.

**Laser Ablation**

Laser ablation is an interstitial technique in which an applicator is used to deliver a high-power density of light (800-1064 nm) to the tissue. The light is both scattered and absorbed by the tissue. The absorption events are primarily near the laser and result in large heating near the laser applicator. Similar to other interstitial heating techniques, cooling of the laser using water or gas is useful for generating larger lesions. In this case, cooling the catheter of the laser prevents charring of the adjacent tissue, facilitating larger applied laser powers to be used to increase the overall size of the lesion. Class IV lasers are used for ablation, which require appropriate laser safety training and equipment, as well as accreditation, and registration with the institution laser safety officer.

Using coaxial catheters, ultrasound or MRI can be used to navigate the laser applicator into position akin to biopsy guidance. Laser applicators and fibers tend to be inherently compatible with the MRI environment; however, MR-dedicated systems do exist. Because there are no large metal components, MRI morphology and functional images are relatively free of artifact. As with FUS, MRTI can be used to both localize the laser and monitor treatment delivery. Often diffusing tip fibers 1 cm in length and 400-600 mm in diameter are available using applied powers of up to 40 W per fiber. The size and rate of ablation is contingent on the wavelength, power, applicator cooling, and local perfusion. Because of this exposure, times and lesion sizes can vary greatly, with times from 90 seconds to several minutes for lesions on the size of 1.5 cm to several centimeters. Generally, lesions are ellipsoidal and centric to the diffusing fiber tip, so multiple fibers and placements may be needed to conform to an irregular shape or large volume. Often, the fiber can be “pulled back” within the cooling jacket to extend the length of the lesion as needed.

Initial feasibility studies using laser for breast cancer have resulted in 13%-91% complete ablation rates. Lesions tend to be smaller than those created using either RFA or microwave ablation. Placing of multiple fibers with multiple pullbacks can extend the procedure time and cost. As with RFA, microwave ablation, and FUS, pain management is a concern.

In conclusion, most clinical trials of breast cancer ablations have been performed with cryoablation or RFA in phase II studies. Successful treatment has been reported as 76%-100% in RFA, 36%-93% in cryoablation, and 20%-100% in high-intensity focused ultrasound cases. RFA requires local analgesia over the pectorals major muscle, sedation or general anesthesia or both, and heat-based methods have been associated with some skin burns or substantial patient discomfort. Cryoablation has the advantages of being a simple procedure with low-cost equipment, a high patient comfort and safety in an outpatient setting, and several previous and pending clinical trials. Finally, studies in animal models and patients undergoing local thermoablative techniques, especially cryoablation, suggest tumor-specific immune responses stimulated by the damaged cells, which may contribute to control of metastases distant from the primary site.

**References**


