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Radiofrequency Ablation of Invasive Breast Carcinomas: A Phase II Trial

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Background: Local ablative therapy of breast cancer represents the next frontier in the minimally invasive breast-conservation treatment. We conducted a phase II trial to evaluate radiofrequency ablation (RFA) of invasive breast carcinomas.

Methods: Consecutive patients from two Mexican Institutions with invasive breast cancers < 4 cm, with no multicentric tumors and no previous chemotherapy were included in this trial. Under ultrasound guidance, the tumor and a 5 mm margin of surrounding breast tissue were ablated with saline-cooled RFA electrode followed by surgical resection. Routine pathologic analysis and viability evaluation with NADPH-diaphorase stain were performed to assess tumor ablation. Procedure-associated morbidity was recorded.

Results: Twenty-five patients were included. Mean patient age was 55.3 years (range 42–89 years). Mean tumor size was 2.08 cm (range 0.9–3.8 cm). Fourteen tumors (56%) were <2 cm. The mean ablation time was 11 minutes using a mean power of 35 W. During ablation, the tumors become progressively echogenic that corresponded with the region of severe RFA injury at pathologic examination. Of the 25 patients treated, NADPH stain showed no evidence of viable malignant cells in 19 patients (76%), with significant difference between tumors <2 cm (complete necrosis in 13 of 14 cases, 92.8%) vs. those >2 cm (complete necrosis 6 of 11 cases, 54.5%) ($P < .05$). No significant morbidity was recorded.

Conclusions: RFA is a promising minimally invasive treatment of small breast carcinomas, as it can achieve effective cell killing with a low complication rate. Further studies are necessary to optimize the technique and evaluate its future role as local therapy for breast cancer.

Key Words: Radiofrequency—Ablative therapy—Breast cancer—Breast conserving therapy.

During the past century, there has been a continued transition toward less invasive local treatment of breast cancer.[1] Initially, this included a shift from the classical en bloc radical to modified radical mastectomy. Observation that moderate-dose radiation was effective in eliminating subclinical foci of breast cancer after mastectomy led to the strategy of breast-conserving therapy. Although mastectomy continues to be appropriate for some patients, a breast-conserving procedure has become the preferred method of treatment for most patients with early breast

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cancer. Conventional axillary node dissection for breast cancer is associated with considerable morbidity, and this has led to the introduction of sentinel node biopsy technique that affords improved staging with minimal morbidity.[2] Following this continuum of conservatism, there is an impetus to continue reducing the morbidity of local tumor treatment.

A major goal of breast-conserving treatment is the preservation of a cosmetically acceptable breast, although a variety of patient, tumor, and treatment factors have been reported to influence the cosmetic results. The amount of breast tissue resected appears to be the major factor.[3] Several investigators are studying the feasibility of percutaneous minimally invasive techniques to ablate breast tumors. Several modalities such as cryosurgery, laser ablation, thermoablation, and high-intensity focused ultrasound have been investigated.[4,5] By minimizing damage and disruption to normal surrounding tissue, the morbidity of local treatment, such as scarring and deformity, can be reduced and the cosmetic result can potentially be improved. With the widespread application of screening mammography, the mean size of breast tumors detected has continued to decrease, which further emphasizes the need for less invasive means for achieving local tumor destruction such as radiofrequency ablation (RFA).[6]

There have been publications of experimental results demonstrating that RFA is feasible in an animal model,[7] so we performed a phase II trial to determine the efficacy and safety of RFA of human breast cancer using the saline-cooled tip electrode.

METHODS

All patients had prior histologic diagnosis of invasive breast cancer established by ultrasound-guided core biopsy for nonpalpable lesions or by needle core biopsy for clinically palpable tumors. Core biopsy had to be adequate for routine pathologic evaluations (grade, estrogen receptor, progesterone receptor, HER-2−neu) because after RFA has been performed, a viable tumor may not be available for these analyses.

Eligibility criteria included age >18 years and tumor size ≤4 cm in diameter, determined by ultrasound (US) measurement. Patients were excluded if there was evidence of multifocal breast cancer or diffuse microcalcifications suggestive of multifocal ductal carcinoma in situ. Patients treated with preoperative chemotherapy were also excluded. The study was approved by the Institutional Review Boards of the two participant institutions, and all patients provided written informed consent.

All patients underwent breast ultrasound preoperatively to determine if the invasive tumor was visible, as it would facilitate ultrasound-guided RFA. The patient could elect to undergo either a lumpectomy or a mastectomy as in both situations the RFA tissue would be available for pathologic review. Sentinel lymph node biopsy (SLNB) was performed for axillary staging in patients with nonpalpable axillary lymph nodes. For SLNB, 1 mCi of technetium-labeled rhenium colloid was injected in the peritumoral area 2 hours before the procedure, and 2.5 cm^3 of isosulfan blue dye (Lymphazurin) were injected in the subareolar region at the end of RFA, according to a previously published technique at our institution.[8]

After general anesthesia was induced, and after previous preparation and draping, the breast tumor was identified with the aid of a high-resolution ultrasound with a linear array, broadbander transducer (Aspen L 7 MHz, Acuson, Mountain View, CA). Under ultrasound guidance, the 17-gauge probe (Elektrotom 106 HiTT, Berchtold, Germany) was inserted in the center of the tumor. With ultrasound imaging in two planes, we ensured that the electrode was present in the center of the lesion. The needle electrode was attached to a 500 kHz monopolar RFA generator capable of producing 200 W power. Grounding was achieved by attaching one grounding pad to the patient's back before the procedure. Tissue impedance was monitored continuously using a circuitry incorporated into the generator. A syringe attached to the system was used to infuse normal saline into the lumen of the electrode, maintaining the temperature of the tip between 70 and 90°C.

The appearance and progression of hyperechogenicity on ultrasound was used to guide the therapy. RF energy was applied to the tissue with initial power setting of 30 W, for three cycles of 3 minutes each. The energy was increased with increments of 5 W to a maximum power of 50 W. Radiofrequency was delivered until the tumor was completely hyperechoic with the aim of obtaining a safety margin of 1 cm around the tumor according to previously published data.[9] If we did not achieve the desired ultrasound effect, after repositioning the tip of the needle, another 3-minute cycle was applied. Saline circulating internally within the electrode cools the adjacent tissue, maximizing energy deposition and reducing tissue charring. To minimize thermal injury to the skin, the breast was carefully positioned in a relaxed form before RFA was delivered.

Following ablation, the needle electrode was removed and 2.5 cm^3 of isosulfan blue dye were injected in the subareolar area. After the SLNB was completed in the usual fashion, standard tumor resection was achieved with either a wide local excision or mastectomy according to the clinical situation and patient's preference. The surgical specimen was oriented and immediately sent fresh to the pathology department.

The margins were inked and the entire resected specimen was divided in 3-mm parallel sections in the area of the ablated breast tumor. The tumor was carefully evaluated for areas of ablation. Features analyzed include coagulative necrosis, burn artifact, and nonablated areas. The central portion and areas determined to lack or have fewer features of ablation were submitted for viability studies. Margins were not submitted to ensure that standard final pathologic examination would not be compromised. The representative sections harvested were immediately snap-frozen in liquid nitrogen for subsequent NADH-diaphorase viability studies. The remaining tissue included the ablated area and macroscopically visible tumor. These were submitted in such a sequential manner that the entire area was submitted for histologic examination by the standard hematoxylin–eosin (H&E) technique. On H&E sections, the tissue was evaluated for the usual parameters of breast cancer, i.e., size, subtype, grade, lymphovascular invasion, in situ component, and the presence of residual tumor in the surgical margin. Negative margins were defined as absence of malignant cells in the inked tissue. In addition, the tissue was analyzed for thermocautery artifact, inflammation, granulation tissue, and the host response to the ablation. Immunohistochemical analysis for hormone receptors was performed in the core biopsy before RFA and was not done in the ablated tissue.

The histochemical enzyme analysis of cell viability is based on the reduction of nitroblue tetrazolium chloride—a redox indicator—by NADH-diaphorase resulting in an intense blue cytoplasmatic staining. The activity of this enzyme has been shown to subside immediately upon cell death. For this analysis, 8 μm unfixed frozen sections were placed on glass slides. Incubation media consist of 1 mL of reduced α-NADH (Sigma-Aldrich Corp., St Louis, MO) at a concentration of 2.5 mg/mL distilled water, 1 mL of phosphate-buffered saline (pH 7.4) at a concentration of 2 mg/mL, and 0.5 mL of Lactated Ringer's solution. Each tissue section slide is covered with 100 μL of incubation media for 15 minutes under aerobic conditions at room temperature. Each slide was then washed in distilled water for 2 minutes. Glass cover slips were then mounted with an aqueous medium. Slides were evaluated for characterization of staining within 24 hours of processing. A section of normal breast tissue was used for positive control, and a section of normal breast tissue placed in phosphate-buffered saline and heated to 100°C was used as negative control.

Following treatment, patients underwent routine surveillance and standard whole breast radiation therapy as part of breast-conservation therapy. Immediate complications were recorded as well as 1-, 3-, and 6-month follow-up. Cosmetic results were assessed in clinic during follow-up visits by means of a four-point scoring system of breast cosmesis[9] with results being appraised before adjuvant radiotherapy was started. This system is subjective and assessed by the patient. Decisions regarding adjuvant systemic therapy were based on the status of the sentinel lymph node, tumor size, and prognostic factors such as ER, PR, and HER2/neu expression as determined by pretreatment core biopsy.

Descriptive statistics were applied. The measurements used for assessing the success of RFA were: (1) the amount of tumor coagulated and (2) the viable cell count. Categorical variables were compared by the chi-square method. Significance was considered at $P < .05$.

RESULTS

Twenty-five patients completed the proposed radiofrequency ablation. Mean age was 55.3 years (range 42–89 years). Mean tumor size assessed by ultrasound was 2.08 cm (range 0.9–3.8 cm). Fourteen tumors (56%) were ≤2 cm. The most common tumor location was the upper outer quadrant in 16 cases (64%), followed by upper inner quadrant of the breast in 5 patients (20%). Three patients (12%) had palpable lymph nodes in the axilla and underwent standard axillary dissection. Twenty-two patients (88%) underwent SLNB: the node was successfully found in all cases and found to be positive in 14 of them (64%). These patients underwent axillary dissection. Histologic analysis disclosed infiltrating ductal carcinoma in 21 patients (84%), infiltrating lobular carcinoma in two patients (8%), and mixed type (ductal and lobular) in two patients (8%). Four patients (19%) with infiltrating ductal carcinoma showed ductal carcinoma in situ (DCIS) associated in <20% of tumor area.

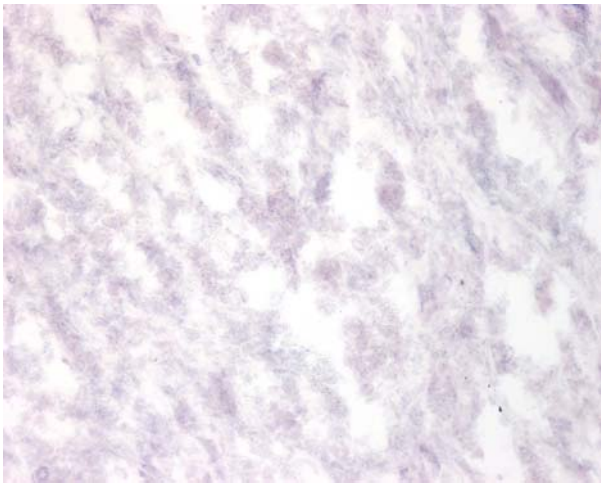

FIG. 1. NADH-diaphorase staining showing no viable cells.

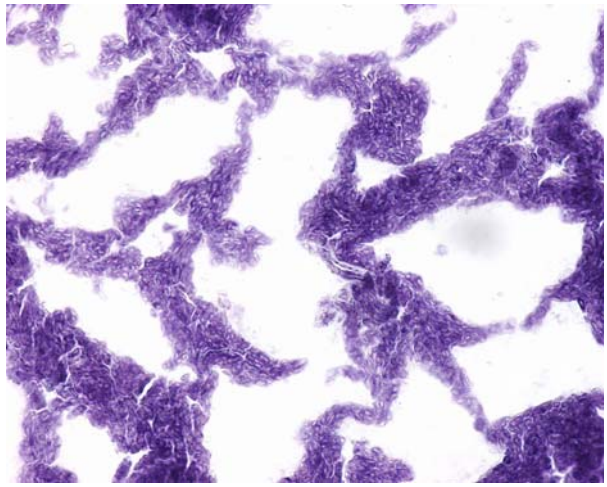

FIG. 2. NADH-diaphorase staining showing absence of tissue ablation with complete viable tissue.

RFA time ranged from 9 to 15 minutes (mean 11 minutes). A median of three cycles and a mean power of 35 W (range 30–55 W) were used to achieve tumor ablation. The tissue during treatment became progressively echogenic, until the tumor margin could not be discerned. The size of ablation measured by ultrasound reached at least 5 mm around the tumor in all cases. Peritumoral injection of technetium rhenium colloid for sentinel node biopsy did not interfere with ultrasound visualization of the tumor.

Fifteen patients underwent breast-conserving therapy, and 10 patients underwent mastectomy. There were no positive margins in any surgical specimen. On H&E examination, the tumor architecture was maintained despite ablation, which allowed pathologic size to be accurately assessed. There was no significant difference between radiologic and pathologic size. The RFA-treated carcinomas showed a range of pathologic findings. Some cases showed elongated nuclei with "smudged" chromatin. All cases showed extensive electrocautery changes with densely eosinophilic stroma.

NADPH viability stain showed no evidence of viable malignant cells in 19 cases (76%) (Fig. 1), with significant difference between tumors smaller than 2 cm (complete necrosis in 13 of 14 cases, 92.8%) vs. those bigger than 2 cm (complete necrosis 6 of 11, 54.5%) ($P < .05$) (Fig. 2).

Overall, RFA was well tolerated, but 2 patients (8%) had a transient elevation of body temperature (37.8°C and 38.1°C, respectively) during the procedure. Three patients (12%) developed superficial skin burning; one of them had elected mastectomy, and in the other two cases a narrow en bloc skin excision during lumpectomy was performed. There was one superficial wound infection that responded to conservative management with antibiotics. At the time of last follow-up all patients treated with breast-conserving therapy subjectively reported excellent (80%) or good (20%) cosmetic result. At a median follow-up of 38 months, 2 patients developed distant metastatic disease: both patients had tumors larger than 2 cm, axillary metastasis, and incomplete RFA in the histopathologic analysis.

DISCUSSION

The results of the present study show that breast tumors smaller than 2 cm can be completely eliminated by ultrasound-guided RFA, but this technique is not effective for larger tumors. Similar to other studies,[10] there was a variation in the time required to achieve complete ablation of the tumor. This variation is thought to result from heterogeneity of the tumor, particularly the differentiating thermal and electrical properties of the breast tissue. Furthermore, breast tissue is known to vary extensively between patients, especially the geometric distribution and proportion of the fat content. The tissue near the electrode is heated primarily by the absorbed electrical energy, while regions further away are mainly heated by thermal conduction. Other factors that have been shown to influence tissue impedance are the proximity of the vessels to the tumor, the body surface area of the patient, and the variation on spatial shapes of the different tumor types (the diffuse growth pattern of

lobular carcinoma versus the spiculated morphology of ductal carcinoma).[11,12]

In our clinical trial, the H&E staining showed complete ablation of the tumor in all but one case of the tumors smaller than 2 cm. Similar results from the NADPH-diaphorase staining were obtained, thus achieving a success rate of 92.8% in this group of patients. However, larger tumors were completely ablated in only 55% of cases. In the initial exploratory study from the Stanford University of California,[13] 5 patients with locally advanced breast cancer underwent RFA under US guidance with LeVeen needle electrode (Radio Therapeutics Corp, Mountain View, CA). All patients showed tissue ablation, and, according to NADPH-diaphorase staining, complete tumor ablation could be demonstrated in 4 of 5 patients with no morbidity. In the pilot study by Izzo et al., using the same electrode, coagulative necrosis was completed in 25 of 26 patients (96%).[14] In this study, the authors included 20 patients with T1 tumors and 6 patients with T2 tumors; median tumor size was 1.8 cm. Similar results were published from the MD Anderson Cancer Center, where sonography confirmed complete ablation of the targeted lesion in 93% (27 of 29), while histologic examination showed that 86% (25 of 29) of the primary tumors (all of them <2 cm) had been completely ablated.[15] One Canadian study reported complete tumor ablation of lesions <3 cm in 19 of 22 patients excised (86%) 2 weeks after RFA, but they pointed caution for 3 positive margins and 5 patients with multifocal disease.[16] Our study compares favorably with these and other pilot studies,[17,18] showing complete ablation in the majority of small tumors, but we demonstrated that RFA is not effective for larger lesions. All studies mentioned used the same electrode for RFA. There are two other studies in addition to ours using saline-cooled tip electrode for RFA; one of them reported complete ablation in 13 of 14 patients (92.8%) with tumors <1.5 cm.[10] The other recent study reported 52 patients who underwent RFA with saline-cooled electrode without excision of the tumor, albeit cytology was obtained. With a short follow-up of only 15 months the authors do not report any tumor recurrence, and cosmetic result were reported as excellent or good in 95% of patients.[19]

The viability data has to be interpreted with caution because of the limitation of tissue analysis. To determine whether or not the tumor was completely ablated, i.e., nonviable, it would have been necessary to completely submit the tumor and margins for NADPH-diaphorase staining. As stated in the Methods, the most grossly viable appearing tissue was submitted for viability study, but limitations in sampling are recognized.

RFA and other local ablative treatments for early stage breast carcinoma are felt to be of limited efficacy in tumors with undefined borders (i.e., infiltrating lobular carcinoma or tumors with extensive intraductal component).[20,21] Cryoablation appears to be less effective because of incomplete freezing and a subsequent high rate of residual disease. In a recent multicenter report, this technique was found to be limited by tumor size and the presence of associated ductal carcinoma in situ.[22] In our trial, 4 patients had tumors associated with up to 20% DCIS in whom complete coagulation necrosis was achieved. Likewise, successful thermoablation can also be achieved for invasive lobular carcinoma (2 patients with "pure" type and 2 patients with mixed pattern in our series) if they are of the circumscribed variety as observed in our series and the one by Fornage et al. from MD Anderson.[15] Nevertheless, if radiofrequency alone was to be used in a future trial, as recently was already done,[19] this cancer type would be excluded as tumor size is often underestimated. Another group that should be excluded as was done in the present study are patients treated with preoperative chemotherapy as there might be clusters of viable cells beyond the palpable mass after tumor shrinkage, which thus results in inadequate local treatment.

In the aforementioned studies and in our clinical trial, NADPH-diaphorase assay was a necessary component for assessing the adequacy of the RFA treatment of breast tumors. However, in routine clinical practice it can be burdensome to perform this assay as it requires tissue to be snap-frozen immediately in liquid nitrogen. Burak et al. used AE 8/18 immunostain and found it to be a valuable marker of viability.[20] Khatri et al.,[10] evaluated paraffin sections by immunohistochemistry for routine proteins (ER, PR, pancytokeratin, Ki67) to determine whether they could potentially serve as a surrogate marker for viability, but they could not demonstrate any reliable correlation.

The common complication reported with the use of RFA for breast cancer is skin burns. Proximity of the tumor to either the skin or the underlying muscle is of concern as it can lead to skin necrosis or chest wall burns. In our series, 3 patients (12%) developed superficial skin burns that required local excision. There is a limitation of our study in terms of assessing skin necrosis. We show that there was no acute skin necrosis, but surgical excision was performed immediately after RFA treatment. We are encouraged by satisfactory cosmetic results in our population, but

acknowledge that to assess skin necrosis better, a delay time period between RFA and resection would be necessary. This evaluation has been done in studies with delayed excision,[10] or no excision,[19] with good cosmetic results. We believe that our technique of positioning the breast to relax tissue was a valuable technical adjunct. Other studies[13–16] used electrodes that require deployment of radial tines that can approach close to the skin and enhance the risk of inducing skin burns. Since the electrode used in the present study and others[10,19] does not require multiple-tine electrode deployment, it further enhances its safety profile. An added benefit of the Elektrotom 106 HiTT, Berchold electrode with the single tip was that we could visualize it easily by sonogram.

Several important limitations were observed with the use of ultrasonography for treatment guidance. Not only is considerable experience required in performing breast ultrasound, but availability of a high-resolution ultrasound is necessary to allow identification of the hypoechoic tumor within the background of extensive echogenic stromal tissue. The conventional gray-scale ultrasound is also limited by its inability to provide real-time monitoring of the adequacy of RFA treatment as the edge of the hyperechoic-ablated lesion is not as well demarcated. The use of contrast-enhanced ultrasound appears to be valuable in monitoring the progression of the thermic lesion as demonstrated in a porcine model of renal RFA.[23]

For ablative therapies to be successful, accurate preoperative assessment of the size of the tumor and the extent of any associated ductal carcinoma in situ is necessary to prevent undertreatment. Also necessary is the availability of a noninvasive method of post-procedure confirmation of complete necrosis. Cytology has been used in a nonresection study after RFA, but the results are limited by sampling error and the very short follow-up of the study.[19] Breast MRI has considerable potential in this regard for preoperative local staging and surveillance.[24] Burak et al.[20] used pre- and post-RFA and magnetic imaging of the breast and found that enhancement is a good surrogate of lack of complete ablation, but the results are limited by the small sample size. Emerging technologies such as micro-CT/PET and positron emission mammography (PEM) may prove to be valuable adjuncts in facilitating ablative therapies.[25,26]

Before RFA alone can be adopted as the unique local therapy, there are several critical oncologic issues that remain to be resolved. These include the effects of adjuvant radiation therapy to the in situ ablated tumor, whether the oncologic outcomes will be equivalent to the current standard breast-conservation therapy and whether the potential cosmetic superiority of percutaneous RFA will be confirmed. If the eventual goal of ablation is to leave the treated tumor in situ, we would be limited by the lack of information on surgical margin. Since breast-conserving therapy has become a viable option for treatment of breast cancer with survival equivalent to mastectomy, the concept of margin assessment has become critical yet not without associated unresolved issues. Several studies show that negative surgical margins do not guarantee complete removal of disease, and likewise histologically involved margin equally does not always indicate persistence of disease.[27] Thus, evaluation of surgical margins is not an absolute indicator of local control, when it is generally recognized that adjuvant radiation therapy will reduce local failure by approximately two-thirds and chemotherapy has been demonstrated to delay development of local recurrence. Thus, in the current era of genomics, perhaps the molecular signature of the primary tumor may assess the biological behavior more accurately than margin evaluation. Examination of these issues in the context of clinical trials is vital for future integration of image-guided minimally invasive local therapy of breast cancer.

In conclusion, several pilot studies including our own have demonstrated that RFA therapy is useful for the local treatment of small invasive breast carcinoma as it produces effective cell killing in a predictable volume with a low complication rate. It is anticipated that image-based minimally invasive breast surgery for small malignant tumors, that are now more commonly encountered, will afford the patient with the advantage of a less painful and aesthetically more pleasing therapeutic modality. A lumpectomy, despite its limitations primarily from its cosmetic viewpoint is still a time-tested standard of care and is a relatively easy operation. Therefore, rigorous research will be needed to evaluate ablative therapies before they can replace lumpectomy. Nevertheless, a combination of image-guided RFA of breast tumor with concurrent axillary staging using the minimally invasive and highly accurate sentinel lymph node biopsy could potentially become the future breast-conserving therapy for breast cancer.

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