Original Study

Breast-Conservative Surgery Followed by Radiofrequency Ablation of Margins Decreases the Need for a Second Surgical Procedure for Close or Positive Margins

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Abstract

Excision of breast cancer followed by radiofrequency ablation is a feasible technique that is used to decrease the need for a second surgical procedure for close or positive margins, and in the long-term, the technique may reduce the incidence of local recurrences.

Background: Excision of breast cancer followed by radiofrequency ablation (eRFA) is a technique designed to increase negative margins in breast-conservative surgical procedures. The objective of this study is to analyze the impact of eRFA in avoiding a second surgical procedure for close or positive margins after a breast-conservative surgical procedure. **Material and Methods:** From February 2008 to May 2010, 20 patients were included. After lumpectomy, the eRFA was performed in the lumpectomy cavity, and biopsies from each margin from the radial ablated cavity walls were obtained. Biopsy samples were assessed for tumor viability. **Results:** eRFA was successful in 19 of 20 patients. In all patients, the devitalized tissue extended beyond a 5- to 10-mm radial depth of the biopsy sample. Overall, 6 patients (31%) had margins < 2 mm, 4 of them with < 1 mm margin. All 6 of these patients had no tumor viability according to analysis of biopsy samples stained with 2,3,5-triphenyltetrazolium chloride. At a median follow-up of 46 months, no local recurrence had been found. **Conclusion:** This study supports the feasibility of eRFA treatment. In our study, the eRFA method has spared 31% of patients from undergoing a re-excision surgical procedure, and it may, in the long-term, reduce local recurrences.

Clinical Breast Cancer, Vol. 14, No. 5, 346-51
Keywords: Breast cancer, Lumpectomy cavity, Radiofrequency ablation, Recurrences, Reoperation

Introduction

Breast-conservative surgery (BCS) has largely replaced mastectomy in patients with early breast cancer, as survival differences between the 2 options have note been shown.[1,2] The objective of BCS is to remove a tumor with negative margins to decrease the chance of local recurrences (LRs). The disadvantage of BCS is the risk of LR, which has been reported to be between 6% and 16%.[3] Obtaining negative margins at the time of surgery decreases the incidence of LR.[4-7] Even with these data, studies have shown that positive margins are found in 20% to 40% of patients.[8] Margin status is considered a predictive factor of LR, and positive margins are related to high rates of residual tumor.[9] In addition, 75% to 90% of LRs occurred at the lumpectomy bed.[10]

Radiofrequency ablation (RFA) is obtained by heat generated from high-frequency alternating currents. As the friction-generated heat from ion movement in the tissues rises the temperature, it causes damage to the cells. The first use of RFA in breast cancer was reported in 1999, and since then, RFA has gained acceptance as a technique for percutaneous ablation of breast cancer. Several reports of percutaneous RFA in patients with breast cancer have shown complete coagulative necrosis of intact tumors in 86% to 100% of

Presented at the 8th European Breast Cancer Conference (EBCC-8), March 21-24, 2012; Vienna, Austria

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Submitted: Oct 27, 2013; Revised: Feb 7, 2014; Accepted: Feb 12, 2014; Epub: Feb 21, 2014

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1526-8209/$ - see frontmatter
http://dx.doi.org/10.1016/j.clbc.2014.02.002

patients.[11-17] Among the problems of percutaneous RFA use is incomplete ablation that has been attributed to technical reasons or underestimation of tumor size by imaging. The increased use of magnetic resonance imaging (MRI) for preoperative assessment of breast cancer has increased the detection of residual tumor after RFA in patients with infiltrating ductal carcinoma.[16,18,19] Excision of breast cancer followed by radiofrequency ablation (eRFA) is a technique that has been developed to ensure negative margins at the time of surgery in patients with early breast cancer. Klimberg et al.,[20] in a pilot trial, showed the feasibility of this technique and the decrease in the need for re-excision of inadequate margins in 41 patient who underwent lumpectomy followed by intraoperative RFA. Of 41 patients, 11 had inadequate margins, but only 1 required re-excision for a grossly positive margin.

The objective of our study was to evaluate the accuracy and effectiveness of RFA on margins to reduce the number of patients requiring second surgeries for close (< 3 mm) or positive margins and to accurately ablate a margin of ≥ 1 cm margin around the tumor bed.

Patients and Methods

Patient Eligibility

For this prospective, nonrandomized trial, patients with a diagnosis of T1-2 N0, unicentric, and unilateral infiltrating ductal carcinoma of the breast who presented in our clinic and required a lumpectomy were included. Patients were recruited from February 2008 to May 2010. Exclusion criteria were neoadjuvant chemotherapy, pregnancy, breast implants, extensive microcalcifications, and tumors located < 1 cm from the skin or the pectoralis muscle. The study was approved by the institutional review board, and patients signed an informed consent form. Breast imaging was performed with mammography and breast ultrasonography. MRI was not performed prior to surgery. Patients completed a subjective cosmetic result survey at baseline and at 6 months. Cosmetic results were recorded on scale of 1 to 6, 1 being not at all satisfied and 6 being extremely satisfied. Assessments based on the Radiation Therapy Oncology Group (RTOG) scale, which records acute radiation morbidity, were performed at 6 and 12 months after the radiation therapy (XRT) and as part of postoperative assessment of the affected breast.

After surgery, all patients received whole-breast irradiation as part of the standard treatment at our institution. Patients were required to come to the clinic for follow-up visits for a minimum of 2 years after the procedure. The first visit was a postoperative follow-up visit occurring within 2 weeks of the surgery. Afterward, patients returned every 6 months for a mammogram, for 2 years. After that, patients returned to the clinic for the standard follow-up protocols. Immediate and late complications from the procedure were recorded.

eRFA Procedure

Once they were in the operating room, patients underwent the standard procedures for a sentinel lymph node biopsy[21] and for a lumpectomy; tissue specimens were sent fresh for tissue banking and for routine processing and margin-width assessment. The lumpectomy was immediately followed by the RFA procedure. The target temperature was set to 100°C for 15 minutes for ablating the tissue cavity. A purse-string suture was performed in the lumpectomy cavity to approach the tissue, and the RFA device (StarBurst XL Semi-Flex, AngioDynamics, Queensbury, NY) was inserted into the lumpectomy cavity.[20] The arrays were deployed into the cavity, and the eRFA was started. Once the procedure was finished, the device was removed from the cavity. Next, 4 perpendicular incisional biopsies of the radial ablated cavity walls (medial, cranial, lateral, and caudal walls) were obtained. These biopsies were obtained to provide anterior to posterior radial tissue slices, approximately 2 cm in radial depth and 0.5 cm in width. With minimal drying and tissue distortion, these 4 biopsy slices were submitted fresh (without fixation) and sent to the pathology department for 2,3,5-triphenyltetrazolium chloride (TTC) viability staining to document the radial depth of the cavity. Careful hemostasis was obtained and all the oil aspirated, and then the cavity was closed according to standard procedure following a lumpectomy.

Pathologic Assessment

The 4 incisional biopsies from the ablated cavity wall were labeled with the patient's name and identifiers, including the cavity wall from which each sample was obtained and immediately sent fresh from the operating room to the pathology department. Care was taken to not dry, wash or rinse with water, crush, or distort the tissue biopsies during handling. A delicate suture marked the lumpectomy cavity edge of each biopsied tissue sample for orientation. The unstained incisional wall biopsies were digitally photographed and then immediately placed in a TTC vitality stain for 1 hour in a 37°C water bath. (TTC staining allows for regions of thermal necrosis to be highlighted and identified using a dehydrogenase enzyme—and cofactor-based reaction that converts the tetrazolium salt to a formazan pigment within viable tissues. This results in a cytochemical color change from colorless to red-orange in tissues with preserved enzymatic activity, in other words, viable tissues.) Following staining, the tissue samples were digitally photographed again. Later, they were fixed in 10% neutral buffered formalin and embedded in paraffin for further hematoxylin—eosin (H&E) standard staining and histological evaluation of the biopsies.

Results

The eRFA technique was successful in 19 patients out of 20. The mean patient age was 66.9 years (range, 46-76 y). The mean pathologic tumor size was 14.7 mm (range, 4-28 mm). Tumor and patient characteristics are shown in Table 1.

In all patients, the devitalized tissue extended beyond the 5- to 10-mm radial depth of the biopsy sample (range, 4-16 mm). Of the 20 patients, 12 of the 19 patients (63%) had negative margins (> 3mm) at the time of the final pathologic assessment. Furthermore, 6 patients (31%) had margins < 2 mm in the final pathologic assessment. All 6 of these patients had incisional biopsies from the cavity wall with no tumor viability detectable after staining with TTC. (Fig. 1) In 1 patient, an invasive carcinoma was found at the edge of the punch biopsy, > 1 cm away from the coagulative necrosis (Fig. 2). This patient underwent a mastectomy.

Intraoperative-margin status was assessed by macroscopic visualization, and frozen section was performed if any margin was considered suspicious. There was no reported positive margin intraoperatively, and reported close margins were taken care of with

Table 1 Patient and Tumor Characteristics

Variable	Patients, no.
Total	19
Tumor Histology	
Infiltrating ductal carcinoma	9
Infiltrating ductal carcinoma + DCIS	8
Infiltrating ductal carcinoma + Others	2
Clinical Stage	
I	14
II	5
Pathologic Stage	
Positive sln	2
Negative sln	17
Grade	
I	6
II	12
III	1
Estrogen Receptor Status	
Positive	18
Negative	1
Human Epiermal Growth Factor Receptor 2 Status	
Positive	1
Negative	18

Abbreviations: DCIS = ductal carcinoma in situ; sln = sentinel lymph node.

the eRFA procedure. Taken together, 31% (n = 6) of patients avoided a second surgery for margins < 1 mm.

All patients underwent whole-breast XRT, and 1 patient also had XRT to the nodal basins.

There was no intraoperative complication from the RFA. In all, 6 patients (31%) had developed a lipid cyst in the mammogram at 1 year after the eRFA. Of these patients, 2 underwent a core needle biopsy at the tumorectomy site because of suspicious areas of recurrence. Pathologic assessment found that both were fat necrosis. Of the patients who underwent core needle biopsy, 1 developed a wound infection that was resolved with antibiotic treatment. At a median follow-up of 46 months, each of these 2 patients still had a persistent lump that corresponded to the lipid cyst, although in 1 patient the size of the lump had reduced. In all 6 patients, the lypid cysts continued to appear on mammographic images.

We did not find any complication related to infection nor skin burn, as the skin is well protected during eRFA because one can visualize the distance from the device to the skin.

Cosmesis, assessed by the subjective cosmetic scale, was self-reported as follows: 13 patients revealed being extremely satisfied (score 6), 4 patients reported a 3, and 2 patients a 4. Patients who developed lipid cysts were less satisfied with the cosmetic results because of the palpable lump that persists over time. By the RTOG acute radiation morbidity scoring criteria, 15 patients (79%) were categorized as good (score 7-8), corresponding to minimal differences between treated and non treated breast. The remaining 4 patients were categorized as fair (4-5), corresponding to obvious difference between the treated breast and untreated breast.

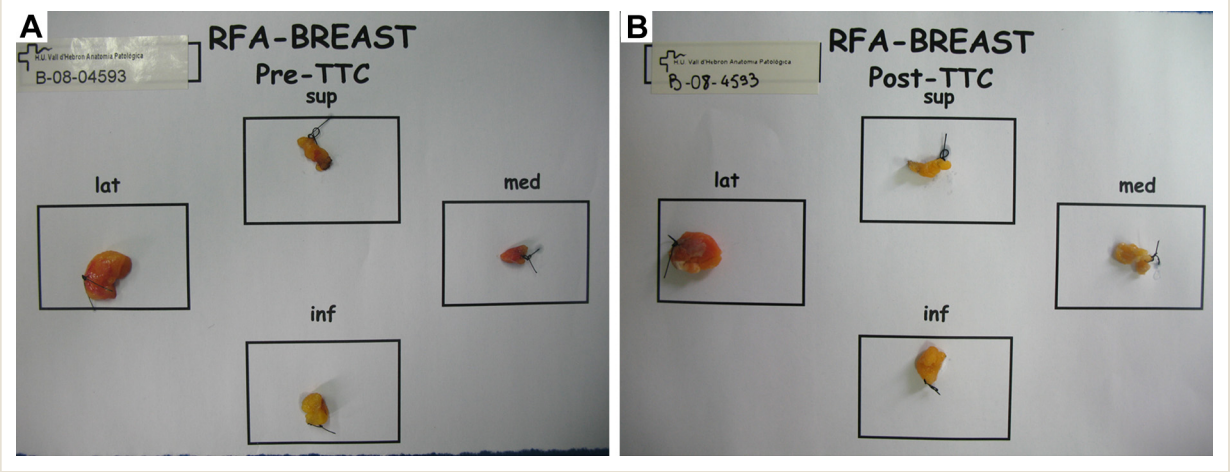
At a median follow-up of 46 months (range, 34-61 mo), no LR had been found.

Discussion

Importance of Margins in BCS

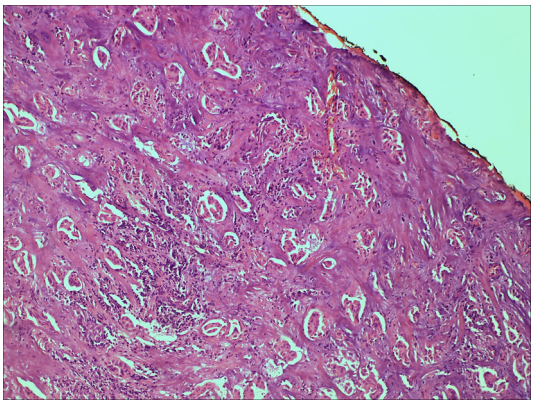
The performance of BCS with negative margins at the time of the first surgery offers the best chance to achieve good cosmetic results in patients with breast cancer. Several approaches have been used to achieve negative margins at the initial surgical procedure, as this has been reported by multiple studies to decrease the incidence of LR.[4-7] Ablative techniques via percutaneous needle have been introduced as a promising and minimally invasive alternative to

Figure 1 Incisional Biopsies of the Radial Ablated Cavity. Examples of the 4 Incisional Biopsies of the Radial Ablated Cavity (A) Before Staining With 2,3,5-Triphenyltetrazolium Chloride (TTC) and (B) After Staining With TTC. No Change in Tissue Color Between the Pre-Staining and Post-Staining Images Indicates a Lack of Viable Tissue



Abbreviations: inf = inferior; lat = lateral; med = medial; RFA = radiofrequency ablation; sup = superior; TTC = 2,3,5-triphenyltetrazolium chloride.

Figure 2 In 1 Case, Ductal Carcinoma Cells Were Present on the Radial Margin of 1 Punch, Marked With Black ink. The Cells Presented Distortion and Artifacts That Were due to the Ablation (H&E, 20 ×)



BCS for local treatment in women with early breast cancer.[11-14] The problem with the percutaneous RFA techniques is that they cannot achieve negative margins in 100% of cases. Patients with extensive intraductal components, lobular carcinomas, or tumors > 2 cm are not well-suited for these ablative techniques.[15,17] Noguchi et al. have reported patients who underwent percutaneous RFA and mammotome biopsy after RFA to assess complete response.[19] In 8 out 19 patients, there was a complete histological response, although reduced nicotinamide adenine dinucleotide (NADH) staining did not demonstrate any viable tumor in the ablated lesions. Although cosmesis was considered excellent or good in all cases, in half of the patients a hard lump was persistent.[22] Another issue of concern is the best way to obtain an image of the residual disease after percutaneous RFA. As different studies have reported, failure in complete tumor ablation can occur when the extension of the lesion is underestimated in the evaluation prior to the technique.[23] The inclusion of MRI results in evaluating the lesion pre- and post-RFA has proved to be effective in determining the presence of residual tumor after RFA, although the number of patients included in the studies is small.[18,19]

Negative margins have been proven to decrease the rates of LR in breast cancer.[4-7,9] Minimizing tumor recurrences in the breast is important, because LR is associated with reduced survival.[24] The controversy lies in what constitutes an adequate negative margin, and this has led to a variation in the rate of re-excision after BCS. Recently, it has been reported that rates of re-excision that ranged from 0% to 70% in a study that included 54 surgeons. Approximately 763 patients out of 1909 (40%) Negative margins were achieved at the first surgical procedure.[25] The issue of whether wider margins affect the LRs needs to be carefully examined. It has been reported that patients with large tumors, positive axillary nodes, extensive intraductal components, palpable tumor, or lobular histology correlate with an increased need for re-excision after BCS. The biologic features of the tumor are also important in determining the risk of LRs. Nguyen et al. have reported that patients with tumors that are negative for estrogen and progesterone receptors and human epidermal growth factor receptor 2 have the highest risk of LR, although this characteristics happens in patients after BCS and mastectomy.[26] Even without consensus on the necessary margin width for adequate local control, the use of eRFA in our study has spared 6 out 19 patients (31%) from having an additional surgery. Additionally, in our study, we assessed the devitalized tissue in the lumpectomy cavity treated by the RFA. We could get devitalized tissue beyond a 5- to 10-mm radial depth of the biopsy sample, so this procedure could be important in those patients in whom a wider clear margin would be appropriate.

Assessing Tumor Viability

We used TTC staining for macroscopic tissue viability assessment. It has been reported that H&E staining of the ablated lesion removed after RFA has not demonstrated complete tumor cell death. The wide range of histologic findings on the ablated area is not well differentiated with H&E staining and the tissue architectural disarrangement, because the high temperatures on the breast tissue do not allow a distinction between dead tumor cells and viable tumor cells.[15] TTC staining allows investigators to identify regions of thermal necrosis by using a dehydrogenase enzyme– and cofactor–based reaction that converts the tetrazolium salt to a formazan pigment within viable tissues.[27] This conversion results in a cytochemical color change from colorless to red-orange in tissues with preserved enzymatic activity (viable tissues). Tissues that lack intact enzymatic activity to metabolize the tetrazolium salt do not stain and remain their native color. After staining, the boundary of the thermal necrosis, if present, can be assessed by identifying red-orange staining in the viable enzymatic tissue or cells. Fresh tissue specimen should be evaluated less than 3 hours post removal from the body. Viable tissue could be assessed successfully in all the patients in our study.

Adjuvant XRT

Patients received whole-breast XRT in this study. From the studies of Holland et al.,[28] BCS with negative margins does not guarantee the absence of residual disease in the breast. The use of XRT after BCS works on the low tumor burden in the breast after BCS. XRT to the breast has been shown to reduce LR in the breast,[1] and it not only substantially decreases the risk of LR, but it also has been shown to moderately reduce the risk of death from breast cancer.[24]

Of patients treated with BCS and XRT for localized carcinoma of the breast, 4% to 25% percent develop fat necrosis.[29] We have seen that with the use of XRT after RFA, 31% of patients developed a lipid cyst in the first year. The concern was that in one-third of these patients, the cysts were palpable. Each of these patients underwent a core needle biopsy for diagnosis, as it was not clear by imaging whether the cyst could be a breast cancer recurrence. Klimberg at el.[16,20] in their study do not report rates of fat necrosis. but the difference with this study is that most of the patients in her study did not receive XRT after eRFA. In the study by Noguchi et al.,[22] percutaneous RFA was performed without lumpectomy, but again patients received XRT after RFA, and half of patients developed a hard lump that was persistent over time. Rates of fat necrosis are higher in patients with XRT after RFA than that which is commonly described after BCS and XRT, probably because the inflammatory process is added when both techniques are used.

When eRFA or percutaneous RFA is performed and XRT is added, patients and clinicians should be aware that the rate of fate necrosis is slightly higher than that without RFA. Another option is doing the eRFA without XRT: Klimberg et al. have reported their study without whole-breast XRT and no LRs in the tumor bed,[20] so probably by avoiding whole-breast XRT the risk of fat necrosis would be reduced with no impact on recurrences. More information will be gathered in the proposed multicenter trial with eRFA and no XRT (ABLATE [Radiofrequency ablation after breast lumpectomy added to extend intraoperative margins in the treatment of breast cancer]).[30]

The complete disappearance of fat necrosis after BCS and XRT is reported to be around 2.6%.[29] In our study the mammographic appearance of fat necrosis persists over the follow up. Even with higher rates of fat necrosis with RFA and XRT, in our study, patients who felt the lump were comfortable in the follow-up once the diagnosis was made.

Accelerated partial-breast irradiation (APBI) is currently being explored as an alternative option to deliver adjuvant XRT after lumpectomy in selected patients with early-stage breast cancer treated with BCS. Recent evidence suggests that irradiating a partial breast volume may be an equally efficacious alternative to adjuvant whole-breast XRT in selected, low-risk patients.[31] To date, several studies support the hypothesis that APBI is safe and well tolerated and results in similar outcomes to those of whole breast irradiation in terms of efficacy and ultimate breast cosmesis, although long-term results are awaited.[32,33]

In our study, all the patients had 1 cm of devitalized area after the eRFA procedure, meaning that the technique will cover the area that is supposed to be treated with the APBI. Whether eRFA could represent an alternative to brachytherapy to the breast needs to be confirmed in prospective trials such as the ABLATE trial, which is recruiting patients.[30]

Conclusion

In conclusion, eRFA is feasible and reduce the need for a second surgery to achieve a negative margin. Long-term studies will provide results on its impact on LRs.

Clinical Practice Points

- In the era of more conservative surgery for patients with breast cancer, percutaneous radiofrequency ablation (RFA) has been described to ablate the tumor although one of the problems of percutaneous RFA use is the incomplete ablation in many studies. eRFA is a technique that has been developed to ensure negative margins at the time of surgery in patients with early breast cancer. Experts groups have shown that eRFA could reduce re-excision surgery in breast cancer patients.
- This study evaluates the feasibility of the eRFA technique and the use the eRFA to reduce the rate of re-excision of close or positive margins in breast cancer. eRFA has proven to be feasible and to reduce the rates of re-excision in breast conservative surgery, although increased lypid cysts have been described after radiation therapy of the breast.
- With the recent evidence that partial breast irradiation may be an equally efficacious alternative to adjuvant whole-breast radiation therapy in selected, low-risk patients, eRFA could represent an alternative to brachytherapy to the breast in selected patients and ongoing propective trials may confirm it.

Acknowledgments

Acknowledgment is made to Dr S. Klimberg for her contribution in teaching the technique and the study design.

Disclosure

This work was supported by a grant from the Fondo de Investigación Sanitaria from the Ministry of Health of Spain (P108/90536). AngioDynamics supplied the radiofrequency generator for the study.

The authors have stated that they have no further conflicts of interest.

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