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# Long-Term Results of Phase II Ablation after Breast Lumpectomy Added to Extend Intraoperative Margins (ABLATE I) Trial

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**BACKGROUND:** Excision followed by radiofrequency ablation (eRFA) is an intraoperative method that uses intracavitary hyperthermia to create an additional tumor-free zone around the lumpectomy cavity in breast cancer patients. We hypothesized that eRFA after lumpectomy for invasive breast cancer could reduce the need for re-excision for close margins as well as potentially maintain local control without the need for radiation.

**STUDY DESIGN:** This prospective phase II institutional review board-approved study was conducted from March 2004 to April 2010. A standard lumpectomy was performed, then the RFA probe was deployed 1 cm circumferentially into the walls of the lumpectomy cavity and maintained at 100°C for 15 minutes. Validated Doppler sonography was used to intraoperatively determine adequacy of ablation.

**RESULTS:** One hundred patients were accrued to the trial, with an average age of 65.02 years  $\pm$  10.0 years. The stages were Tis (n = 30); T1mic (n = 1); T1a (n = 9); T1b (n = 27); T1c (n = 22); T2 (n = 10); and T3 (n = 1). Grades were I (n = 48); II (n = 29); and III (n = 23). Seventy-eight subjects had margins  $>2$  mm (negative), 22 patients had margins  $\leq 2$  mm, of which 12 were close and 3 focally positive, which, at our institution, would have required re-excision (only 1 patient in this group had re-excision). There were 6% post-operative complications, and 24 patients received radiation therapy (XRT). During the study mean follow-up period of 62 months  $\pm$  24 months (68-month median follow-up) in patients not treated with XRT, there were 2 in-site tumor recurrences treated with aromatase inhibitor, 3 biopsy entrance site recurrences treated with excision and XRT to conserve the breast, and 2 recurrences elsewhere and 1 contralateral recurrence; all 3 treated with mastectomy.

**CONCLUSIONS:** Long-term follow-up suggests that eRFA may reduce the need for re-excision for close or focally positive margins in breast cancer patients, and eRFA may be a valuable tool for treating favorable patients who desire lumpectomy and either cannot or do not want radiation. A multicenter trial has been initiated based on these results. (J Am Coll Surg 2014; 218:741–750. © 2014 by the American College of Surgeons)

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**Abbreviations and Acronyms**

|      |                                                |
|------|------------------------------------------------|
| BCS  | = breast conservation surgery                  |
| eRFA | = excision followed by radiofrequency ablation |
| RTOG | = Radiation Therapy Oncology Group             |
| WBI  | = whole breast irradiation                     |
| XRT  | = radiation therapy                            |

Standard therapy for breast cancer often requires a multimodality approach that may include surgery, radiotherapy (XRT), and adjuvant systemic therapy. The paradigm of lumpectomy followed by XRT was a major shift in the treatment of breast cancer, offering better cosmesis while maintaining equivalent local and systemic recurrence compared with modified radical mastectomy.<sup>1,2</sup> Especially in rural areas, women living far from radiotherapy facilities often do not undergo breast conservation surgery (BCS) or worse, undergo BCS and do not complete their prescribed XRT course.<sup>3</sup>

Nearly 90% of recurrent disease occurs within 1 cm of the primary tumor.<sup>4-7</sup> So irradiation of the peritumoral cavity (accelerated partial breast irradiation) has been proposed and has provided equivalent local control rates to whole breast irradiation (WBI) in selected patients.<sup>8</sup> Further, accelerated partial breast irradiation via targeted intraoperative radiotherapy for breast cancer (the TARGIT-A trial) in a large international, multicenter, prospective, randomized, noninferiority phase 3 trial was shown to be equivalent to WBI.<sup>9-12</sup>

Unfortunately, numerous studies have failed to identify a subgroup of breast cancer patients in whom radiotherapy can be completely avoided.<sup>13-15</sup> Most notably, the National Surgical Adjuvant Breast Project (NSABP) B-21 randomized trial showed that in patients with favorable hormone-sensitive breast cancer <1 cm there was a 16% 8-year local recurrence rate and a 20% rate by 14 years with lumpectomy alone followed by tamoxifen alone compared with XRT+tamoxifen with 3% and 10%, respectively.<sup>13</sup> In addition, multiple studies have indicated the superiority of negative margins in maintaining local control.<sup>16</sup> Yet the rate of repeat operations to achieve negative margins remains unacceptably high (20% to 40%).

Radiofrequency ablation (RFA) is currently approved by the US Food and Drug Administration (FDA) for ablation of subcutaneous tissues by delivering a high-frequency alternating current into the surrounding tissues, causing ionic vibration and frictional heating of the tissue surrounding the electrode, resulting in coagulative necrosis.<sup>17</sup> This led naturally to the introduction of RFA as a tool applied after standard lumpectomy to the peritumoral cavity subcutaneous tissue to extend the margin for 1 cm.

Klimberg and coworkers,<sup>18-22</sup> through a series of laboratory, preclinical, and clinical trials, established that excision followed by RFA (eRFA) of the lumpectomy cavity provides a consistent 1-cm zone of ablation around the cavitary tumor bed, and therefore the best opportunity to achieve intraoperatively negative margins in patients with breast cancer. Used in this way, we hypothesized that eRFA may reduce unnecessary re-excision as well as provide equivalent protection against local recurrence without XRT in selected patients. We present here the long-term results of our single-institution, prospective, nonrandomized phase II trial of eRFA alone for local breast cancer therapy.

**METHODS****Patients/eligibility criteria**

From March 2004 to April 2010, data on the clinical use of excision of breast cancer followed by intracavitary hyperthermic ablation (eRFA) were collected in a prospective database managed by a team of researchers including breast surgical oncologists, a radiation oncologist, a pathologist, and a biostatistician at the Winthrop P Rockefeller Cancer Institute in order to determine cosmetic results and toxicities associated with its use and short-term efficacy. Under an Institutional Review Board-approved protocol, women older than 50 years of age with a diagnosis of invasive breast cancer, with tumors <3 cm and clinically negative nodes, were included in this study. These eligibility requirements mirror those of the European Society for Radiotherapy and Oncology guidelines.<sup>23</sup> Patients with clinically palpable nodes, skin involvement, or those receiving presurgical chemotherapy were excluded. All patients underwent standard lumpectomy followed by RFA. Patients with positive nodes or aggressive disease were offered WBI.

**Study procedure****Magnetic resonance imaging**

When possible, a rotating delivery of excitation off-resonance (RODEO) MRI was scheduled before surgery to evaluate for residual and multicentric disease, determining eligibility for conservative breast surgery. All images were obtained with a 1.5-Tesla MRI imager using the RODEO pulse sequence, pre- and post-gadolinium contrast (0.1 mmol/kg), high-resolution, 3-dimensional images (256 × 256 × 128, 5-minute scan time). If definitive biopsy-proven multicentric disease was noted on MRI, the participant then proceeded to standard of care with mastectomy.

**Lumpectomy**

Standard lumpectomies were performed under general anesthesia using an image-guided<sup>24</sup> or needle localization

technique.<sup>25</sup> After removal of the specimen by the surgeon, it was sent to the pathology department for routine processing. Intraoperatively, ultrasound was used to assess the specimen and if there was a close margin, then a concomitant shaved margin in the cavity was excised before application of RFA. Close or focally positive margins did not require re-excision per protocol. Margins with more than focal involvement were recommended to be re-excised.

### **Radiofrequency ablation procedure and Doppler monitoring**

Intraoperatively, after standard lumpectomy, patients underwent intracavitary RFA (eRFA) using the RITA Medical Systems Starburst XL RFA probe (RITA Medical Systems).<sup>22,26</sup> Because RFA is currently FDA-approved for ablation of subcutaneous tissue, eRFA follows standard tumor excision for the purpose of creating an additional tumor-free zone via hyperthermia instead of further surgical removal. One or more absorbable purse-string sutures were used to reduce the lumpectomy cavity to approximately 1 cm. The skin was retracted with sutures to prevent potential steam injury. The RFA probe was then deployed into the perimeter of the cavity at the level of the tumor bed and the RFA tines to a depth of 1 cm into the tissue and heated to 100°C for 15 minutes.<sup>18</sup> The RFA was positioned and monitored under Doppler ultrasound guidance to assure a 1-cm intracavitary ablation zone. A 12.5-MHz ultrasound probe was used to follow the ablation zone during surgery to record adequacy of the ablation as well as monitor a safe distance from the skin.<sup>27</sup> After a cool-down period of 1 minute, the purse-string suture was released and the device was removed from the lumpectomy cavity, which was closed in layers with absorbable suture.

### **Final pathology**

All lumpectomy specimens were sent to pathology for hematoxylin and eosin staining and evaluation. Specimens were weighed and measured and the surgical margins were inked. Margins >2 mm were considered negative. A close margin was defined as being <2 mm.

### **Cosmetic outcome**

At 2 postoperative weeks, all patients were evaluated with the point scoring system of breast cosmesis from the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria, which rate the breast as excellent (treated breast almost identical to untreated breast), good (minimal difference between the treated and untreated breast), fair (obvious difference between the treated and

untreated breast), or poor (major functional and esthetic sequela in the treated breast), rated on a scale of 1 to 4 after eRFA and before any other therapy.<sup>28</sup> The LENT-SOMA,<sup>29</sup> commonly used by the RTOG to score post-radiation symptoms subjectively and objectively, was performed between 6 months and 12 months. Using this scale, the breast is assessed by 4 separate criteria: subjective symptoms, objective signs, management of signs and symptoms, and the findings of special analytic investigations. In this system, all 4 aspects play a role in defining the overall level of late radiation toxicity. Patients who received WBI post eRFA were then compared with those who received eRFA alone.

### **Lymphedema**

Patients were measured at 6 months and 12 months after eRFA for lymphedema using arm measurements 10 cm above and 7 cm below the antecubital fossa. Subjective symptoms or an objective measurement of >2 cm in girth were considered lymphedema.

### **Statistical methods**

Data were collected and analyzed in a prospective database using Microsoft Excel (Microsoft Corporation). Descriptive statistics were performed on age, tumor size, margins, and recurrences. Disease-free survival was defined as the time from surgery to either breast cancer recurrence or death. Probabilities for disease-free survival were determined using the method of Kaplan and Meier. Computations were carried out using Stata for Windows, Release 10 (StataCorp LP).<sup>30</sup>

## **RESULTS**

### **Study patients**

One hundred patients were accrued to the trial. The average age was 65.02 years  $\pm$  10.0 years. Disease stages were: Tis (n = 30); T1mic, (n = 1); T1a, (n = 9); T1b, (n = 27); T1c, (n = 22); T2, (n = 10); and T3, (n = 1). There were 48 grade I patients, 29 grade II, and 23 grade III. Seventy-eight of the patients had hormone-sensitive tumors; 8 had insufficient tumor for analysis, 14 patients had hormone receptor negative tumors, and 3 were Her2neu.

### **Excision followed by radiofrequency ablation**

Of the 100 patients registered to the trial, 77 patients underwent eRFA alone; 9 of these went on to have mastectomy for positive margins or undetected multicentric disease. This group of 77 patients was compared with the 23 patients who received adjuvant XRT after eRFA for

unfavorable disease including positive nodes. Figure 1 demonstrates the outcomes of these patients.

### Adjuvant therapy

Seventy-two patients consented to start hormonal therapy. In addition, 17 patients took an doxorubicin-based chemotherapy. Eleven patients to whom further treatment was recommended refused any systemic therapy.

### Lumpectomy margins

Seventy-eight subjects of the total group had margins  $>2$  mm (negative), 22 patients had margins  $\leq 2$  mm, of which 12 were close ( $<1$  mm) and 3 focally positive, which at our institution would have required re-excision (only 1 patient in this group had re-excision). Seven patients underwent mastectomy for frankly positive margins and 2 decided on mastectomy after undergoing eRFA. So, 68% of patients with close or focally positive margins (15% of total) avoided re-excision.

### Locoregional recurrence

During the study follow-up period of  $62 \pm 24$  months, with a median time of 68 months in patients not treated with XRT, there were 2 true tumor recurrences and 2 elsewhere recurrences in the ipsilateral breast, as well as 3 needle biopsy skin tract recurrences. None of these patients had close, focally or grossly positive margins. There was 1 contralateral recurrence in the eRFA group. There were no regional recurrences within the follow-up period.

### Disease-free and overall survival

There were 5 nonbreast cancer-related deaths in the eRFA-alone group over the 5-year period, with an overall survival in this group of 93% at 5 years. Five-year disease-free survival for eRFA was 88%. Disease-free and overall survival of the patients receiving WBI was 83%, with 3 patients dying with metastatic disease; 2 of these had local recurrence. One patient died of heart disease.

### Cosmetic outcomes

#### Two-week evaluation

Patients scored their cosmesis at their postoperative visit ( $n = 83$ ) after eRFA and before any other therapy. Using the RTOG acute radiation morbidity scoring criteria, the average score was  $3.3 \pm 0.7$ . A score of 4 was defined as excellent. Of all recorded scores, there were 37 excellent, 39 good, and 7 fair. No patients considered themselves to have poor outcomes.

### Six- to 12-month evaluation

Patients scored their quality of breast surgery outcome at 6 months using the SOMA-LENT evaluation. If a 6-month evaluation was not available, then the 12-month evaluation was used for the purposes of comparing the 2 groups.

The average SOMA-LENT score for evaluated patients receiving XRT ( $n = 17$ ) was  $5.4 \pm 3.6$  vs  $1.5 \pm 1.8$  ( $n = 68$ ) for those undergoing only eRFA,  $p = 0.0001$ . The major difference in scores centered on long-term pain issues in patients receiving WBI, as subjectively perceived by the patient and objectively measured by the use of pain medicines.

In 44 patients, the ablation zone was partially or easily identifiable on the 6-month mammogram.

At this time point, only 1 patient presented with lymphedema resulting from an axillary lymph node dissection and radiation for advanced disease.

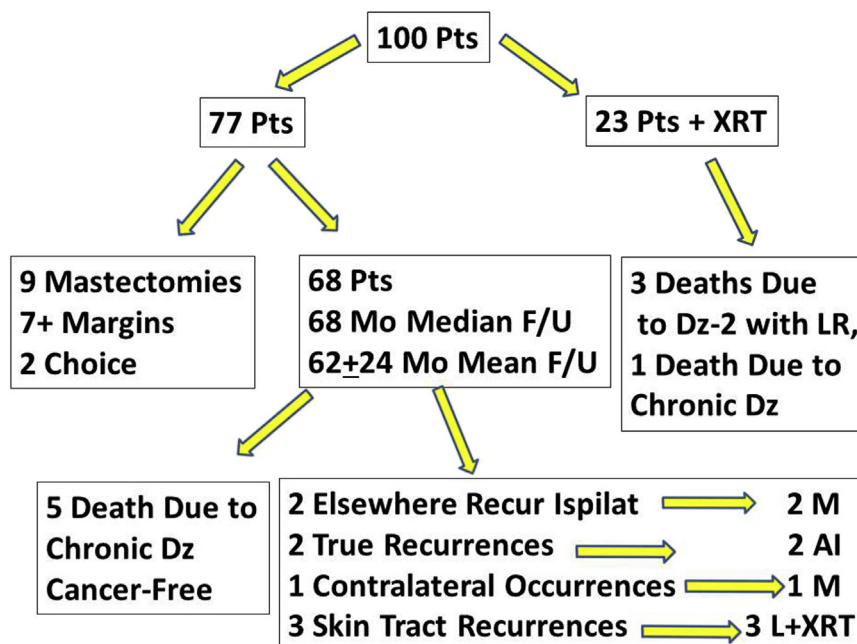
### Complications

There were 6% postoperative complications due to a minor wound dehiscence, hematomas, or infection. Only 2 patients initially accrued to the study (not in 100) were not able to complete eRFA at the time of surgery, 1 due to generator failure and the other due to a flap that was too thin.

## DISCUSSION

Breast conservation is the preferred treatment for breast cancer. However, BCS often requires repeat surgery to obtain negative margins, causing some deformity and inferior cosmesis, which is then further decreased by routinely prescribed adjuvant radiation. Recent studies have recorded a moderate or larger decrease in the size of the irradiated breast at 5 years.<sup>31</sup> In addition, it is estimated that only 70% to 80% of patients receive the prescribed radiation therapy, putting patients at risk for recurrence. Still others choose mastectomy due to limited access for rural areas and/or too much time away from their rural or remote livelihood.<sup>3</sup>

Since BCS began, surgeons have wondered if there was a group of patients in whom radiation could be omitted. In fact, there are 14 randomized control trials that evaluated the omission of radiotherapy in BCS and 1 meta-analysis that resulted in no clearly defined low risk group.<sup>32</sup> In the Oxford overview of more than 19,000 patients, adding WBI reduced local recurrence from 27.2% to 8.8% at 10 years.<sup>33</sup> From another point of view, more than 70% without it didn't have recurrence. Also noted in the overview was the 21% relative risk increase in deaths unrelated to breast cancer in the



**Figure 1.** Outcomes of the 100 patients in the trial. AI, aromatase inhibitor; Dz, disease; F/U, follow-up; L, lumpectomy; LR, local recurrence; M, mastectomy; Pts, patients; XRT, radiation therapy.

irradiated group. One could postulate that modern techniques, and especially partial breast irradiation, would mitigate such an increase in deaths. Indeed, intraoperative radiation does reduce this apparent radiation-induced death as seen in the Targeted Intraoperative Radiotherapy vs Whole Breast Radiotherapy for Breast Cancer (TARGIT) trial, with an overall increase in nonbreast cancer-related deaths of 3.5% with WBI compared with 1.4% in the intraoperative XRT group ( $p = 0.0086$ ), deemed largely attributable to more deaths from cardiovascular causes and other cancers.<sup>10</sup>

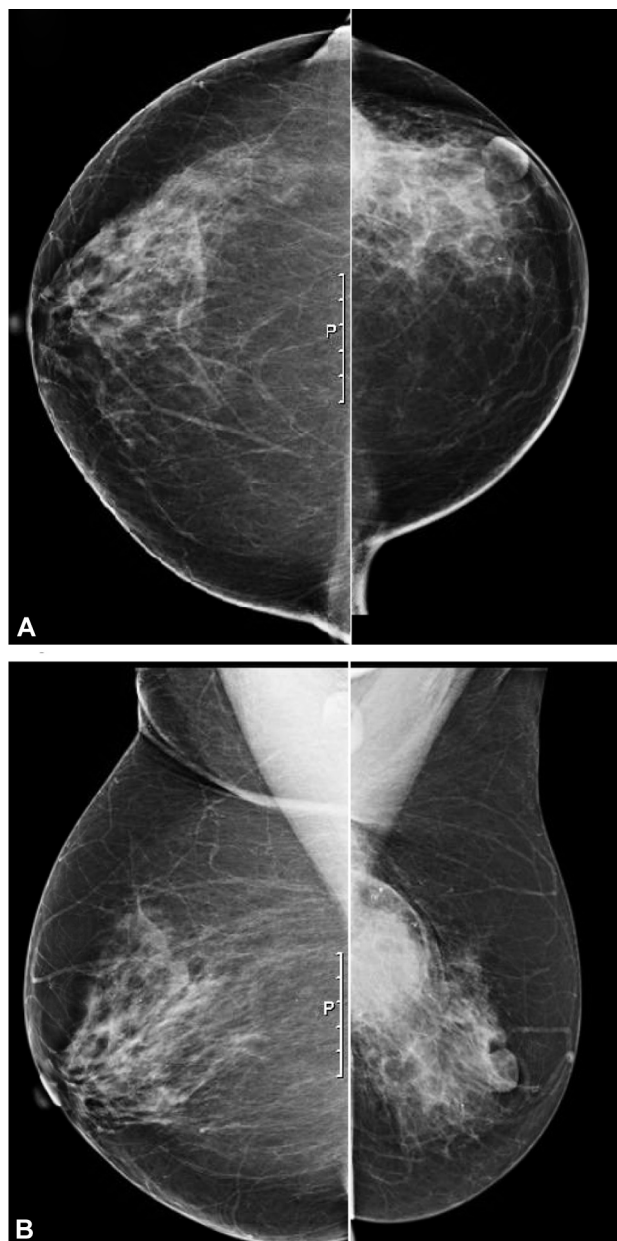
The purpose of this study was to explore eRFA as a possible treatment alternative for selected patients, with the goal of reducing re-excision rates and providing similar local control as with WBI but with reduced morbidity and cost. Completing local therapy intraoperatively would be a significant advantage psychologically as well as to the workforce, the elderly, the poor, and the rural patients who may not have ready access to radiation facilities or had contraindications such as collagen vascular disease or previous radiation. The other advantage is that the prescribed local therapy would be definitely completed, which is not the case in the nearly 20% to 30% of patients prescribed XRT but never wind up receiving it.<sup>3</sup> Increased deaths secondary to radiation and unrelated to breast cancer would also be negated with the use of eRFA.

## MARGINS AND LOCOREGIONAL CONTROL

One of the concepts of intraoperative treatment of the margin is that no one knows better than the surgeon where the tumor was actually situated within the breast wound. Therefore intraoperative therapy should be superior to postoperative treatment. This concept is supported by the TARGIT-A trial, in which patients treated at the time of the original operation were compared with those having second operation specifically for administering intraoperative XRT. Patients treated at the time of the first operation with intraoperative XRT fared better than those treated during a second procedure (2.1% vs 5.4% 5-year local recurrence).<sup>11</sup> All patients in this study were treated at the time of the original operation.

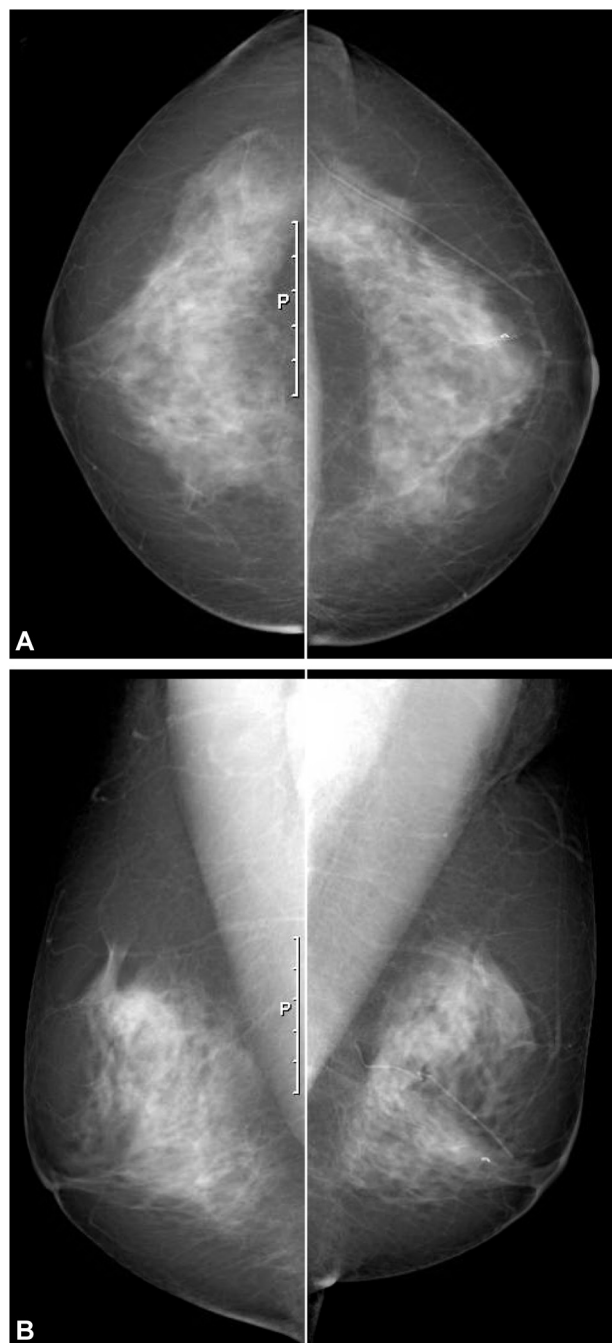
According to our practice, patients with margins <2 mm necessitate re-excision for optimal local control. In the literature, re-excision for close or positive margins ranges from 20% to 40% and even higher with needle-localization breast biopsy.<sup>24</sup> Of the 100 patients in this study, 22% had close, focally positive, or positive margins. Of these patients, 7 had mastectomy for positive margins as well as 2 by preference (Fig. 1). Therefore, 68% of the patients with close or positive margins avoided further surgery. Twenty-three patients went on to WBI deemed necessary for larger tumor size, positive nodes, or apparent aggressive disease.





**Figure 2.** (A) Cranial caudal views of patient 5 years out from radiation therapy. The mammogram demonstrates a substantial size difference in the left irradiated breast compared with the contralateral breast. Also note the outline of fat necrosis at the excision followed by radiofrequency ablation sight. (B) Medial lateral oblique view of patient in (A).

Of the 69 patients in this group who were treated with eRFA alone, there were 7 ipsilateral breast tumor recurrences (Fig. 1). There were 2 true recurrences presenting in the bed of the tumor, presenting in an 82- and a 91-year old. Both of these patients were not initially prescribed hormonal therapy and remain free of disease without any further intervention. There were also 3 patients



**Figure 3.** (A) Cranial caudal view of patient 5 years out from excision followed by radiofrequency ablation alone, demonstrating dystrophic calcifications at the biopsy site but little change in size or density of the breast. (B) Medial lateral oblique view of patient in (A).

more than 5 years out from their initial therapy who presented with recurrence at the entrance site of the core biopsy needle. All 3 had resection of this site and underwent WBI. This has prompted us to either include the incisional biopsy entrance site in our lumpectomies or perform a

separate punch biopsy of the track during the initial surgery. In addition, there were 2 elsewhere recurrences in the breast in patients who did not receive an MRI before eRFA. One was a subareolar ductal carcinoma in situ and the other was a mucinous carcinoma; both patients underwent mastectomies. Mucinous tumors are low grade and are easily missed by mammography and even MRI. There were no regional recurrences.

### Survival

Overall 5-year survival in our eRFA group is 93%, with 5 deaths due to chronic disease or other cancer. The lower survival seen in the radiated group of patients (overall and disease-free, 83%) is expected because of more aggressive disease presentation. Disease-free survival at 5-year average follow-up is 88%, with no reported distant disease. Eight patients in this group required further therapy; all but 2 are free of any disease. The remaining 2 elderly patients were treated only with aromatase inhibitor with regression of local disease without resection.

### Cosmesis

The eRFA resulted in a good to excellent RTOG acute cosmesis scores at 2 weeks after surgery in 92% of patients. This compares favorably with the 70% good to excellent results using the same scale reported in the literature.<sup>32</sup> In the 6- to 12-month LENT-SOMA (Late Effects Normal Tissue Task Force subjective, objective, management, and analytic) evaluation, patients who had received radiation fared significantly more poorly on the chronic cosmesis follow-up score, in part due to better cosmesis with eRFA, but in large part due to subjective and objective signs of pain.

### Toxicity

There is no question that on mammography, eRFA leaves a clear ring of fat necrosis (Figs. 2 and 3.) This area is palpable when the lumpectomy is more superficial but is smooth to palpation, much like an implant, and is smooth on mammography. Despite this, the eRFA fared well on the chronic cosmesis scale compared with results in the literature on irradiated breasts. Only 44% of patients had a barely or clearly palpable area at the biopsy site. Patients accept this local change in their breast as well as any scar. A potential benefit noted by our mammographer was that because most recurrences recur at the lumpectomy bed, the imager knows the very sight at greatest risk.

Wound complications are acceptably low for our institution. Monitoring with intraoperative Doppler helps the surgeon avoid the potential for burns to the skin.

The low rate of lymphedema in this study is mainly due to the initiation of the ARM (axillary reverse

mapping) protocol, which maps and protects the lymphatics draining the arm and which we have shown decreases lymphedema.<sup>34</sup> Lymphedema was seen in only 1 patient, who had an axillary node dissection without axillary reverse mapping and who also had additional XRT.

### Charges

The necessity of offering routine WBI or partial breast irradiation to maintain local control has resulted in a substantial cost to the health care system and inconvenience, work-loss, and morbidity to the patient. In our institution, charges are made to the patient undergoing eRFA using the CPT codes for intracavitary hyperthermia (77620) and ultrasonic monitoring of the ablation (76940) as well as the radiofrequency probe and the generator. Total charges for adding RFA are estimated at \$6,295 as compared with \$47,061 for WBI and \$24,981 for partial breast irradiation. Charges for re-excision are about \$13,000. The eRFA cost is one-fourth the cost of partial breast and greater than one-seventh the cost of WBI. This is in addition to the cost-savings attributable to the increased percentage of negative margins during the first operation obviating the need for re-excision. In this study, 65% of the patients who entered into the study avoided WBI or mastectomy. More than two-thirds of patients with close or positive margins avoided re-excision due to eRFA. This equates to approximated 15% of the whole group. In the present economy this represents substantial cost savings considering the number of patients treated worldwide.

### Limitations

This study was a small, single-institution nonrandomized study on eRFA in a selected patient population. The study was designed as a pilot study to gain safety and efficacy information. The RTOG cosmetic scales, although not designed for nonradiated patients, were used to gain insight into its usefulness in this setting for a randomized trial of eRFA and radiation. This information will be used to make power calculations to move forward with a prospective randomized trial. Of note, this trial is as large as the original brachytherapy trials as well as the few intraoperative radiation studies reported in the United States.

### CONCLUSIONS

A plethora of studies have failed to define a group of patients who can forgo radiation to complete BCS. Genomic studies may help define such suitable patients, but as of yet, have not been reported in nonradiated patients. Long-term follow-up suggests that RFA added to standard BCS (eRFA) may not only reduce the need for re-excision for close or focally positive margins in breast cancer patients, but may obviate the

need for WBI in favorable patients. Excision followed by radiofrequency ablation may be a new paradigm for treating favorable patients who desire lumpectomy but who either cannot have or do not want radiation. A multicenter trial has been initiated based on these results.

### Author Contributions

Study conception and design: Klimberg, Hardee, Adkins, McCarthy, Makhoul, Korourian

Acquisition of data: Klimberg, Ochoa, Henry-Tillman, Boneti, Adkins, McCarthy, Tummel, Malak

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Critical revision: Klimberg, Ochoa, Hardee, Adkins, McCarthy, Tummel, Korourian

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## Discussion

**DR KIRBY BLAND** (Birmingham, AL): It's a pleasure to discuss this recent contribution by Dr Klimberg and her colleagues from the University of Arkansas and their research foundation because this represents their latest advancement in the management of this common neoplasm of the breast. I further congratulate the authors, as they have added immensely to scientific discovery with this technological advancement. Let me emphasize that this represents a phase 2 study, a single-institution pilot evaluation. And I am certain that the authors would recommend that immediate application of the technique is not warranted at present until we move this to a phase 2B or a phase 3 study that is prospective in both scope and outcome. But this represents as large an original trial as the local irradiation trial, the Intraoperative Radiation Therapy (IORT) trial, and it's considerably larger than most of the anecdotal trials that were conducted in IORT in the United States.

Your objectives and the analysis, Dr Klimberg, are commendable. And outcomes equate to those of whole breast irradiation (WBI) in select cohorts of the analysis. Moreover, if you look at radiofrequency ablation (RFA), it is equatable to intraoperative radiation therapy (RT), as this new technology may actually contribute to further reduction of irradiation-induced cancers. And as you recall from the target trial, those other nonbreast cancers, as well as cardiovascular disease, were twice as great in the whole breast irradiation group as they were in the IORT.

So this has considerable advantage among those groups. But as you stated in the manuscript, your local regional therapy has considerable advantage for treatment of that patient in various subpopulation types, such as the elderly and the person in a remote area, who's going to have to be transported in daily for RT, perhaps the uninsured, as well as particularly, the working patient. And further, the satisfaction of completing therapy has immeasurable advantage, I think, which is not the circumstance with at least 25% of our patients who are postmenopausal requiring radiation therapy and virtually all premenopausal patients who require radiation therapy after breast conservation for invasive disease.

Finally, I think it is a significant advantage. You briefly commented on the psychological aspects of a single operative procedure

and getting it through, like you did in almost three-quarters of your patients. I have some questions.

First, your cohort comparisons for RFA to that of the more aggressive disease group subsequently treated with radiation need further clarification, as does the group that required additional surgery. You stated that additional surgery was required in 10%. That's really not surprising if you find multicentric disease or if you find positive surgical margins. However, the 23 patients in whom you discussed regarding adjuvant RT after RFA for unfavorable disease, could you tell us their ultimate fate in terms of survival at 5 years? I know you don't have 10-year survival, but could you tell us the differentials in outcomes of these patients? Expectantly, these are the ones who would have the worst outcomes in your analysis.

Secondly, with follow-up at 5 years, a 68-month median follow-up, the staging for the patients in this analysis was notable. Thirty percent of them were in situ disease and 58% of them were under 2 cm, with a considerable number larger than this. Is there a difference in progression of ductal carcinoma in situ (DCIS) in the group that are compared with those in the under 2-cm invasive side?

Third, I think your survival rate is commendable at 5 years for those 77 patients who require only RFA. But could you tell us, if you look at WBI patients, overall (I know you didn't do a prospective analysis of that group) what you would project equivalence for stage of disease in those patients?

Finally, the last thing we talk about is, frankly, the cosmetic outcomes. Your cosmetic index score is actually as good, if not superior, to that with WBI. Radiation is not a good thing for soft tissue disease, and it's certainly not a good thing in the breast in terms of cosmesis. It reduces volume, symmetry, and, as you showed in some of your pictures today, it causes increasing concavity of the incision as well as increasing density. So what outcomes do you expect over time in this 68-month follow-up for these patients? What is your caveat today that you would recommend to the surgeon after this phase 2 study? Is there anything we should take away to move this technology more rapidly to clinical application?

**DR STEPHEN GROBMYER** (Cleveland, OH): Management of surgical margins and reducing morbidity of multidisciplinary treatment are 2 very important issues in breast cancer research, which Dr Klimberg and colleagues are addressing with the use of RFA as an adjunct to lumpectomy. Radiofrequency ablation, like single-dose intraoperative radiation therapy, offers the potential of completing all local therapy for patients during the operative event and eliminating the need for, and the subsequent side effects of, WBI. I have 4 questions for Dr Klimberg.

1. Radiofrequency ablation results in a 1-cm zone of coagulative necrosis around the lumpectomy cavity. Could the same results be achieved by just removing an additional centimeter of tissue around the lumpectomy cavity?
2. In terms of in-breast recurrence in lumpectomy patients, you observed several needle biopsy site recurrences, which historically have been very uncommon in breast cancer. We have not seen this in patients having single-dose intraoperative radiation therapy, nor was it reported in lumpectomy trials omitting radiation therapy, such as CALGB 9343. Was there something