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A novel technology for margin extension and local control in breast conservation surgery: Saline-coupled intraoperative radiofrequency ablation (SIRA)

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A B S T R A C T

Importance: Breast-conserving therapy (BCT) results in reoperation in ~20 % of cases due to positive margins, and a 7–13 % recurrence risk at 5 years persists despite negative margins and radiation. Enhancing margin treatment is critical to reducing local recurrence and improving survival.
Objective: To optimize and evaluate the performance of a Saline-coupled Intraoperative Radiofrequency Ablation (SIRA) device in producing uniform 1 cm ablations in lumpectomy cavities and compare it to prior-generation RFA technology in previous clinical studies.
Design, setting, and participants: This case series (2018–2023) included 55 mock lumpectomies performed on prophylactic mastectomy or cadaver breasts under an IRB-approved protocol. Inclusion required disease-free, sufficient-volume breast tissue with patient consent.
Results: 55 ablations were performed on breasts from 44 female patients. The SIRA produced an ablation depth of 1.0 ± 0.2 cm (mean, SD), no significant difference between margins ($p = 0.056$). No significant difference in ablation depth across the following: BI-RADS breast composition ($p = 0.212$), age ($p = 0.188$), height ($p = 0.643$), weight ($p = 0.522$), tissue volume removed ($p = 1.000$), breast surgery history ($p = 0.246$), chest chemotherapy/radiation history ($p = 0.477$), or surgeon ($p = 0.579$). Significant difference in depth and variance between the SIRA and previous-generation technology ($p < 0.001$ and $p = 0.016$), with SIRA significantly deeper and more uniform.
Conclusion: Lumpectomy followed by SIRA could reduce positive margin rates and treat additional tissue, resulting in reduction in re-excision rates and serve as a potential alternative to radiation therapy.

1. Introduction

Breast-conserving therapy (BCT) is the preferred management for most patients with early-stage invasive breast cancer [1,2]. BCT typically comprises Breast-Conserving Surgery (BCS) followed by adjunctive Whole Breast Radiation Therapy (WBRT). Achieving negative surgical margins in BCS is important as it reduces local recurrence risk and impacts survival [3–6]. However, approximately one in five cases require costly reoperations due to positive surgical margins, increasing post-operative complication risks [7–10]. Routine pathology examines only 1/1000th of the margin edge, and over 25 % of cases still have residual disease in the reexcision margin despite initial negative pathologic margins [11]. Even after 5 years disease-free post-adjuvant therapy, residual risk of recurrence remains: 7 % for stage I, 11 % for stage II, 13 % for stage III [12], suggesting that negative margins are not the only indicator of long-term outcomes and additional treatment into the tissue could be beneficial.

WBRT remains burdensome, and as a result many women choose mastectomy due to WBRT's side effects [13], [-16] poor cosmesis [17], and the need for daily facility visits [18]. As a result, 15–30 % of BCS patients fail to complete the recommended radiation treatment [19]. Accelerated partial breast irradiation (APBI), including Intraoperative Radiation Therapy (IORT), targets the tissue adjacent the lumpectomy where most recurrences occur, offering similar local control to WBRT

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with shorter treatment time and fewer side effects [20–29]. However, APBI still involves high costs and radiation-induced side effects [30,31].

One proposed treatment alternative is "eRFA", or Excision followed by Radio-Frequency Ablation (RFA). RFA delivers high-frequency alternating current to heat and ablate the surrounding tissue, thus killing residual cancerous cells [32]. eRFA can reduce reoperations and provide local control without radiation, but prior studies were limited by older RFA needle technology designed for non-breast solid tumors [33–37]. A specific *Saline-coupled Intraoperative Radiofrequency Ablation* ("SIRA") procedure and technology was developed to address the shortcomings of the initial eRFA procedure and technology. The SIRA device (Innoblative Designs, Inc., Chicago, IL, USA) is a novel FDA breakthrough designated device designed for the treatment of lumpectomy cavities. It features a spherical applicator with bipolar electrodes, coupled with saline to cool, prevent char, and extend energy to gaps between the device and the tissue. This study aimed to evaluate the SIRA's repeatability and uniformity in human breast tissue, comparing it to previous generation needle RFA technology used in prior clinical trials.

2. Methods

2.1. Test methods

The study was designed in three phases: Settings Development (n = 22), Confirmation Study (n = 25), and Device Comparison Study (n = 4).

In Settings Development, ablation settings were optimized by varying time and power, with a linear model created to analyze how factors such as power, duration, age, weight, height, and fat content influence ablation depth, based on the hypothesis that individual patient characteristics could significantly impact thermal response. Two breast density models were analyzed: Group 1 BI-RADS breast composition score A and B (Fatty & Scattered Fibroglandular) and Group 2 BI-RADS breast composition score C and D (Heterogeneously Dense and Extremely Dense). An equation for optimizing settings was calculated using a regression analysis and a Box-Cox transformation to target a 1.0 cm ablation depth.

The Confirmation Study used the fixed optimized settings in prophylactic mastectomy samples from different patients to assess the repeatability, uniformity, and accuracy of SIRA to create an approximately 1 cm deep ablation in a mock lumpectomy cavity, under an IRB-approved protocol at Northwestern University. Inclusion criteria included: female; subjects 18 years or older; subjects scheduled to receive standard-of-care prophylactic mastectomy; subjects with sufficient volume of breast tissue for the protocol; and subjects who understand and can provide written informed consent. Exclusion criteria included: subjects who had mental, physical, or medical conditions indicating they should not participate; subjects participating in other clinical studies that may impact the participant safety or validity of data; subjects who were pregnant or lactating; subjects with one or more clips implanted in the studied breast; or subjects that had previous surgery on the breast that may affect the protocol as determined by study investigators. Written consent was obtained from all participants whose tissue was used. The Device Comparison Study performed the same procedure in fresh cadaver breast tissue provided by different patients with both the SIRA device and the RITA Starburst XL device (AngioDynamics, New York, USA), the needle device used in the majority of eRFA studies [33–37].

2.2. Device placement and surgical technique

In the Settings Development phase and the Confirmation Study, a breast surgeon (KB) performed a mock lumpectomy using a standardized technique to simulate clinical resection. A 5 cm incision was made after removal of the prophylactic mastectomy specimen on the "back table" on all mock lumpectomies. A video was made at the beginning of the study in order to standardize the cavity creation. A cavity was created using needle-tipped electrocautery and measurements of the cavity were taken. The goal was to obtain a tight fit around the SIRA. Once the cavity was created and the SIRA was inserted with good conformity around the entire spherical surface, a running full thickness skin stitch was placed to secure the device within the cavity. Ultrasound was then used to measure the thickness of the breast tissue surrounding the SIRA.

In the Confirmation Study, another surgeon (SK) was added to assess technique variability.

In the Device Comparison Study, mock lumpectomies were created in cadaver tissue aimed at replicating the methodology of previous studies (see Fig. 1) [35]. Ablations were conducted using the following settings: SIRA optimized settings from Setting Development and Starburst XL settings per previous studies [35]. A Levene two variance test with a CI of 95 % was used to compare the variance in ablation depth for each margin between devices. A two-sample *t*-test was used to compare the mean ablation depths between devices.

2.3. Analysis of tissue samples

For each procedure in the mastectomy model, three tissue samples were taken from each of the six standard margins (Posterior, Anterior, Superior, Inferior, Medial, and Lateral), resulting in 18 ablated tissue slides and one control slide. Samples were inked, stained with Hemoxylin & Eosin, and microscopically examined to assess the ablation zone, percent-fat estimation, and sample length before and after fixation. Tissue shrinkage during the fixation process has been reported to be approximately 11 % in various tissue types [38]. Shrinkage for this study was calculated for each sample during histological processing and used to adjust the final ablation depth for in vivo accuracy. Fig. 2 shows the typical histological slides defining the ablation, transition, and normal zones in ablated breast tissue.

In the Device Comparison Study, eight tissue samples were taken from standard margins (Posterior, Anterior, Superior, Inferior, two from the Medial, and two from the Lateral), and one control. This sampling method showed ablation depth in each plane of the cavity for both devices. Tissue shrinkage was not measured for this study, so the depths could not be adjusted for shrinkage.

The ablation depths reported for all studies include both the necrotic zone and transition zone. The same board-certified pathologist (LB) conducted analysis of all samples.

3. Results

3.1. Demographic data

The Setting Development Phase included 22 mock lumpectomies from 19 female patients' mastectomy breasts. The Confirmation Study included 25 mock lumpectomy cavities from 23 female patients. For the Device Comparison Study, multiple ablations were performed on breasts from two female cadavers. The data in Table 1 describes the demographics across all ablations.

3.2. Settings Development: optimizing ablation settings

A general linear model was created using the mean ablation depth as the dependent variable. (S = 0.166, R-sq = 56.87 %). Height, weight, and duration were statistically significant predictors (p = 0.040, 0.006, and 0.006, respectively). Age, BI-RADS breast composition score, and power were not statistically significant (p = 0.213, 0.090, and 0.968, respectively). Only three of the 22 procedures (13.6 %) in the Settings Development Phase were in Group 1 (BI-RADS breast composition A and B). A regression analysis was performed using only power and duration as variables, because these are settings that can be controlled by the device. The optimized setting for 1.0 cm ablation depth was determined to be 80W for 22 min.

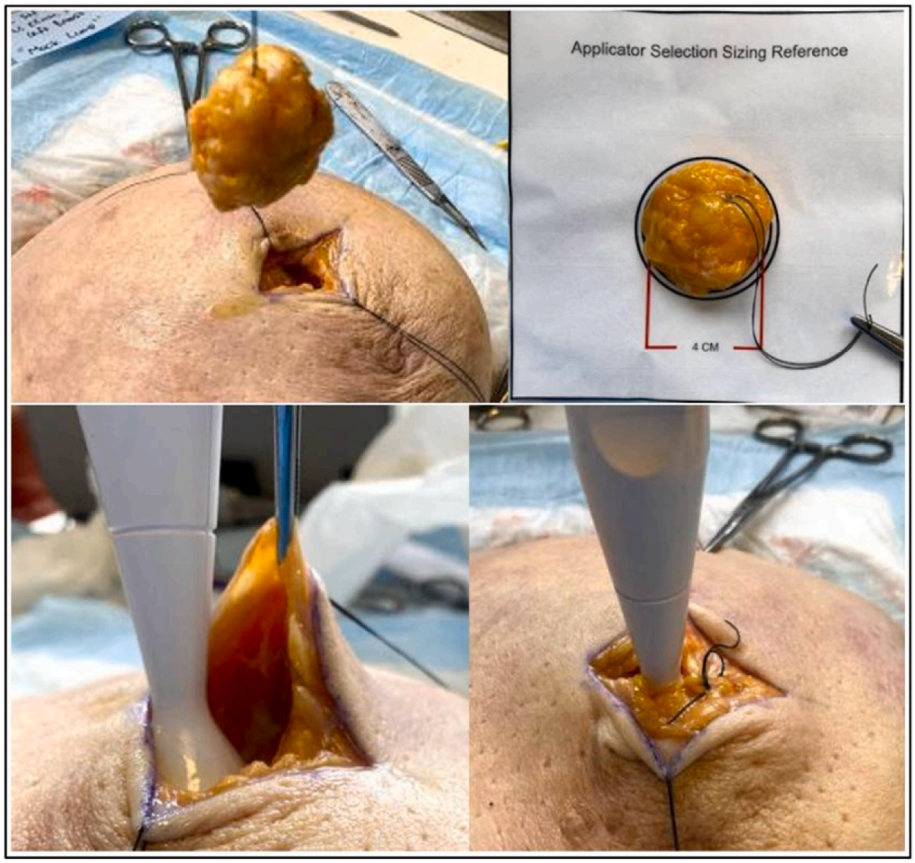

Fig. 1. Simulated lumpectomy procedure. Lumpectomy specimen (3–4 cm diameter) removed. SIRA placed within cavity, sutured in place, and skin retracted to protect from steam and excess hot saline.

3.3. Confirmation Study

In the Confirmation Study, 25 ablations on 23 patients using optimized settings yielded an average pre-fixation ablation depth of 1.0 ± 0.2 cm (mean, SD). Of the samples, 72 % were categorized in Group 2 (BI-RADS breast composition C and D). There was no significant correlation between ablation depth and patient demographics: BI-RADS breast composition score ($r(23) = -0.259$, $p = 0.212$), patient age ($r(23) = 0.272$, $p = 0.188$), patient height ($r(23) = 0.098$, $p = 0.643$), and patient weight ($r(23) = -0.134$, $p = 0.522$). Note, the patient's height and weight are no longer significant factors for ablation depth. The one-way ANOVA showed no significant correlation between ablation depth and surgical factors: breast surgery history ($F(1,23) = 1.41$, $p = 0.246$), history of chest chemotherapy/radiation ($F(1,23) = 0.52$, $p = 0.477$), or the surgeon performing the ablation ($F(1,23) = 0.32$, $p = 0.579$). Finally, there was no correlation between the volume of tissue removed and the depth of ablation ($r(18) = 0.110$, $p = 0.644$).

A One-way ANOVA found no significant depth difference between margins ($F(5,19) = 2.21$, $p = 0.056$). See Fig. 3 for results.

3.4. Device Comparison Study

Ablations by SIRA and Starburst XL devices averaged depths of 0.7 ± 0.2 cm and 0.4 ± 0.3 cm, respectively, without tissue shrinkage adjustment. Fig. 4 shows uniformity differences between the devices, showing all 8 margin measurements for each sample. All margins of the cavities treated by the SIRA device showed varying depths of ablation, while several Starburst XL margins had limited-to-no ablation.

A Levene's test found a significant difference in ablation depth variance ($F = 6.15$, $p = 0.016$) and a two-sample *t*-test showed significant difference in ablation depth ($t(46)$ 5.21, $p < 0.001$) between the SIRA and Starburst XL ablations.

4. Discussion

While BCT has many benefits for women with breast cancer including faster recovery and improved quality of life compared to mastectomy, there are still some drawbacks to BCT including the inability to ensure clear margins at the initial surgery and negative aspects from radiation [5,7,39]. Disparities in access to BCT exacerbate these challenges, disproportionately affecting rural, low socioeconomic, and black patient populations [39–41]. These disparities often lead to inequitable outcomes, as patients from underserved communities face systemic barriers to guideline-recommended therapies, such as radiation, and RFA post-lumpectomy could help decrease the inequality in outcomes [39–48].

The inability to ensure clear margins during the initial surgery frequently necessitates re-operation, resulting in an increased cost of approximately $16,072 to the patient, an 89.1 % higher risk for multiple complications, inferior cosmesis, and negative psychological outcomes [7,36]. Furthermore, many patients may be candidates to forgo radiation based on factors such as pregnancy, age, prior radiation exposure, tumor size, and genetic predispositions [49–51]. For those who can receive radiation therapy, there are negative side-effects (e.g., skin burns, other cancers, and heart and lung disease), high costs, and lack of adherence to the therapy, resulting in 15–30 % of patients never receiving the prescribed treatment [19]. Some studies have shown non-inferiority of 1-week to multi-week WBRT, but further studies are needed to determine its limitations to breast cancer radiation precision [52].

The SIRA device aims to directly reduce positive margin rates and provide enhanced margin clearance during the initial lumpectomy. By

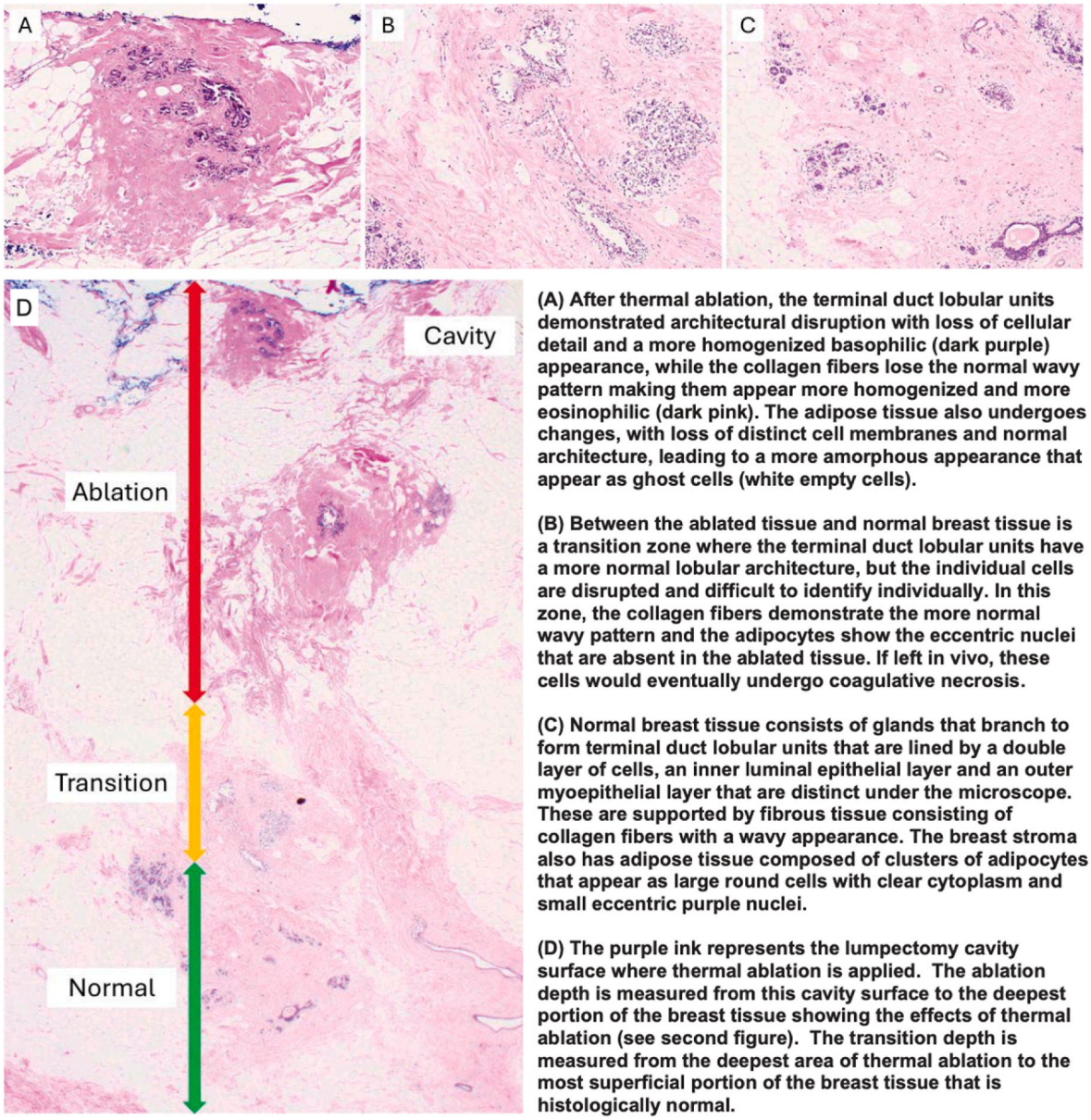

Fig. 2. Sample histology slides defining the ablation, transition, and normal zones in ablated breast tissue. Pictures (A), (B), (C) taken at 100X magnification. Picture (D) taken at 20X magnification.

utilizing eRFA technology, SIRA's unique design provides a uniform approximate 1 cm ablation around the lumpectomy cavity, reducing positive margins, and aiming to reduce reoperation rates and the need for radiation therapy for select patients, such as patients that are eligible for brachytherapy or partial breast irradiation. Some patients, such as those undergoing sentinel lymph node biopsy of the axilla or axillary lymph node dissection, may benefit from radiation that the lower axilla is exposed to during WBRT plus cavity boost. However, it has been suggested that eRFA could replace the cavity boost in many cases [35]. This study presents the findings on the first device designed specifically to reduce positive margins in a breast cavity by treating the margin during lumpectomy surgery.

Klimberg et al. were the first to study the eRFA method [35]. They performed ablations using a needle device designed for solid tumor ablation in the prophylactic mastectomy model, the same model used in this study, reporting a 5–10 mm depth of ablation. This lead to a subsequent 100 patient single-institution prospective study where eRFA with no adjunctive radiation therapy resulted in the reduction of re-excisions by 68 %, reduction of post-treatment pain by 4x compared to patients receiving radiation, good or excellent cosmesis in 92 % of patients, survival rate of 93 % at 5 years, and 2.9 % true ipsilateral local recurrence rate [36]. Subsequently, Klimberg et al. initiated the ABLATE Phase II multi-center trial to assess recurrence rate of 242 patients treated with eRFA [37]. At 44 months, re-excisions were <5 %, in-breast recurrence was 2.9 %, cosmesis was good or excellent in 89 % of patients, and chronic pain was 5x less in patients who underwent eRFA alone verses patients who underwent WBRT.

Additional evidence highlights the potential of eRFA technology to reduce positive margins and thus reduce re-operation rates and improve patient outcomes. Rubio et al., studied eRFA in a 20-patient prospective single-arm study using a similar methodology as Klimberg et al., except biopsy samples were collected in vivo to measure the depth of ablation and all patients still received WBRT [34,36]. Rubio et al. found that eRFA spared all the patients who would normally require surgical re-excision from a second surgery, there were no RFA-related complications, and at 46 months median follow-up no local recurrence had

Table 1
Demographic Characteristics of Individual Ablations (total n = 44 patients, 51 ablations).

	Optimizing Ablation Settings (n = 22)	Confirmation Study (n = 25)	Device Comparison Study (n = 4)
Clinical Characteristics, mean (SD)			
Patient Age, years	45 (7.3)	46 (15.0)	57 (5.7)
Patient Height, inches	65 (2.6)	64 (2.3)	67 (0.7)
Patient Weight, lbs	162 (27.5)	161 (35.0)	143 (3.5)
BI-RADs Breast Composition Score, No. (%)			
Group 1 Low Density	3 (14)	7 (28)	NA
Group 2 High Density	19 (86)	18 (72)	NA
Clinical History, No. (%)			
Previous Surgeries or Biopsies	7 (32)	7 (28)	0 (0)
Previous Radiation Therapy or Chemotherapy	5 (23)	7 (28)	2 (50)

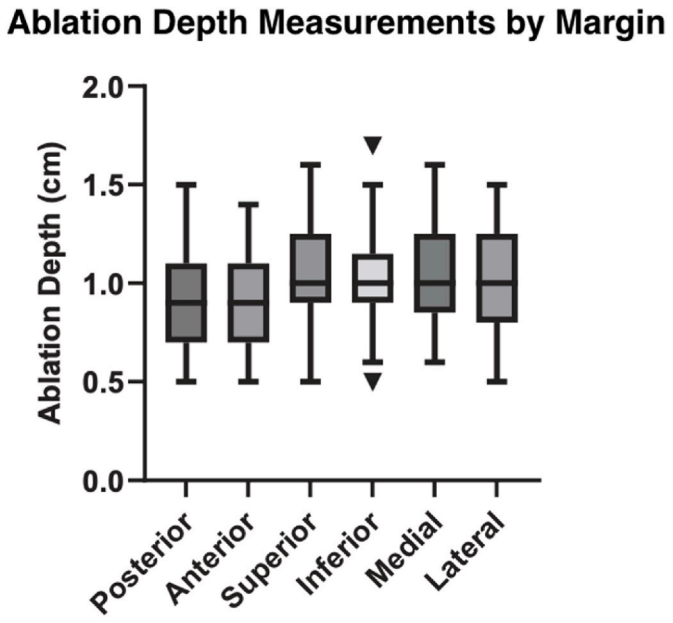

Fig. 3. Mean adjusted pre-fixation ablation depth across all margins for the 25 Confirmation Phase ablations.

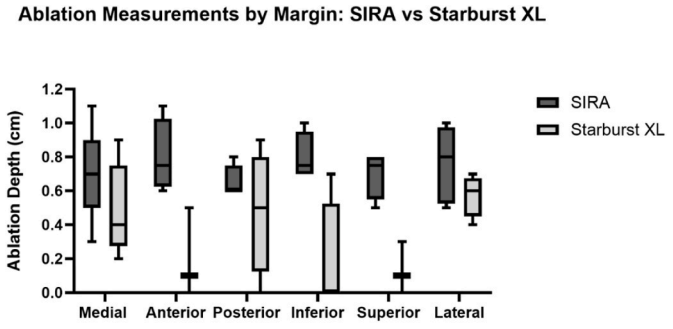

Fig. 4. SIRA vs. Starburst XL Post-fixation Ablation Depths in Cadaver Tissue.

been found. Similarly, Mazure et al. ran a 40-patient single center non-randomized eRFA study resulting in 0 % re-operations and 5 % complications for the RFA group (compared to 12.5 % and 10 %, respectively, in the control group which received no RFA), concluding that eRFA is a safe and effective method for achieving tumor-free margin while avoiding increased complications [33].

To date, over 400 patients have been treated with eRFA in both single and multi-center studies, and have shown promising results, including favorable long-term recurrence and survival rates [33–37]. The devices used in previous studies were designed to percutaneously puncture and ablate a solid mass, not fit a lumpectomy cavity, which may explain why an incomplete ablation of some surfaces is possible (Fig. 4). Additionally, despite positive clinical outcomes, many surgeons found the needle devices too difficult and burdensome to use in the breast cavities. In contrast, SIRA's design is easy to use and fits the lumpectomy cavity's shape, achieving uniform ablation across all margins, which is critical to ensure all microscopic cancers are treated in the surrounding approximate 1 cm margin. The SIRA device's consistent ablation depth across diverse patient demographics, including different BI-RAD breast composition scores and adjuvant treatment histories, suggests the device's broad applicability. The SIRA device's consistent ablation depth across different surgical variables, such as the size of the tissue removed or the surgeon performing the procedure, suggests the device can produce repeatable results. It is promising that with the inclusion of additional samples in the dataset (samples with a wider height and weight range than those initially studied in the Settings Development phase), factors such as height and weight no longer significantly affected ablation depth, demonstrating this was just an early artifact of the relatively low sample size from the Settings Development phase of the study. In future studies, height and weight could be a factor in overall cosmesis and therefore should be tracked.

These findings indicate that eRFA with SIRA could reduce positive margin rates and treat an additional zone of tissue, resulting in downstream positive effects such as a reduction in re-excision rates and potentially serve as an alternative to radiation therapy. This approach may particularly benefit older, low-risk patients, as suggested by the PRIME II study, which showed manageable recurrence rates without radiation [53,54]. Furthermore, the SIRA device is an important tool for BCT because current methodologies to assess the margins, such as cavity shavings, frozen section analysis, and intraoperative imaging for residual cancer cells, do not always accurately detect the entirety of the margin for residual microscopic cancer, thus exposing the patient to long-term residual disease [9,11,12].

5. Limitations

The primary limitation of this study is its small sample size, which reduces statistical power and may not represent the broader patient population. The overrepresentation of BI-RADS breast composition Heterogeneously Dense and Extremely Dense breast tissue samples may also skew results and limit generalizability. Larger sample sizes and in vivo testing are needed for validation.

6. Conclusions

Results of this study show that Saline-coupled Intraoperative Radiofrequency Ablation can be used to ablate a controlled margin of tissue, achieving a clinically relevant depth of 1 cm. This work suggests SIRA may achieve potentially superior clinical outcomes with better usability in eRFA procedures compared to the studies using limited existing technology [33–37]. With further clinical testing, the SIRA device may provide a reduction in positive margin rates, reduce BCS reoperations, and offer a one-time non-ionizing therapeutic alternative to radiation therapy in select patients, thus reducing healthcare costs and improving patient care.

CRediT authorship contribution statement

Alyssa Bailey: Writing – review & editing, Supervision, Project

administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tyler R. Wanke:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Rhea Verma:** Writing – review & editing, Writing – original draft. **Thomas Kurth:** Investigation, Formal analysis. **Conor Shanley:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Erin Mohr:** Investigation. **Scott Irving:** Investigation. **V. Suzanne Klimberg:** Writing – review & editing, Conceptualization. **Luis Blanco:** Writing – review & editing, Resources, Investigation. **Swati Kulkarni:** Writing – review & editing, Resources, Investigation. **Kevin Bethke:** Writing – review & editing, Resources, Investigation.

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