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Thermal Ablation as an Alternative to Standard Breast Conserving Surgery in the Treatment of Invasive Ductal Carcinoma of the Elderly

Dani Ducharme

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By

Danielle Mae Ducharme

Masters Advisor: Kristen Lindvall, PA-C

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Abstract

Background An aging population means an inevitable increase in cancer diagnoses, and thus, a novel solution is needed to address this looming problem. Within the field of breast cancer, thermal ablation has emerged as a promising alternative to surgical excision. As a minimally invasive treatment, it significantly reduces the morbidity and mortality for geriatric patients, as well as healthcare costs overall.

Purpose The purpose of this analysis is to understand the utility of thermal ablation for the treatment of invasive ductal carcinoma. Specifically in the context of elderly patients, it is determined if this treatment modality is superior to traditional breast conserving surgery.

Methods A comprehensive literature review was conducted using Augsburg University Lindell Library database, Google Scholar, PubMed, ScienceDirect and Wiley Online Library using the search terms breast cancer, percutaneous thermal ablation, cryoablation, radiofrequency ablation, high-intensity focused ultrasound, microwave ablation, laser ablation, histopathology, margin evaluation and geriatric. Inclusion criteria was studies published after 2015 using thermal ablation as primary treatment of breast cancer. Exclusion criteria were studies published prior to 2015 and patients were provided neoadjuvant therapy.

Results Cryoablation and radiofrequency ablation are the most effective in achieving complete tumor ablation and preventing local recurrence. Laser ablation, microwave ablation and high-intensity frequency ultrasound are in their infancy of development and warrant further research.

Conclusions Thermal ablation is a reasonable alternative to surgical excision in the elderly and those unsuitable for surgery. Application of these techniques will be crucial to meet the healthcare demand of an aging population in the near future.

Key words Thermal ablation, cryoablation, RFA, LA, MWA, HIFU, breast cancer, IDCA, elderly

Thermal Ablation as an Alternative to Standard Breast Conserving Surgery in the Treatment of Invasive Ductal Carcinoma of the Elderly

Introduction

The lifetime risk of developing breast cancer is 1 in 8 women.[1] The pervasiveness of this disease makes it the leading cause of cancer related death in females, and the second most frequently diagnosed malignancy around the world.[2] In the United States alone, it is estimated 290,000 new cases of breast cancer will be diagnosed in 2022.[1] The global rise in cases coincides with the expansion of screening programs and imaging technology. More importantly, however, these advances increase the likelihood of identifying tumors earlier in their development, thereby providing patients with a highly favorable prognosis. The magnitude of this trend is illustrated by a 2021 meta-analysis: it reports nearly half of all diagnosed breast cancers measure less than 2 cm upon diagnosis, which equates to an excellent 5-year-survival-rate of 98%.[3]

Surgical excision endures as the gold standard of primary intervention for breast cancer; however, over the past four decades, trends have opted towards utilizing less invasive techniques. From the radical and nipple sparing mastectomy, the lumpectomy evolved as the latest customary approach to breast conserving surgery.[2] Reducing the volume of removed tissue lessens patient morbidity and preserves aesthetics, without jeopardizing the effectiveness of treatment.[3] Yet, the unyielding demand for modesty is pushing the field towards avoiding the operating room altogether. A promising frontier is the use of thermal energy to destroy tumor cells. Application of either hypo- or hyperthermic temperatures can be performed through the skin, presumably without the need for general anesthesia. The most studied percutaneous thermal ablation techniques include cryoablation, radiofrequency ablation (RFA), laser ablation (LA),

microwave ablation (MWA) and high-intensity frequency ultrasound (HIFU).[4] These novel methods very precisely obliterate a designated tumor volume, without compromising healthy surrounding tissue. As an alternative to surgical resection, thermal ablation can lower costs for both patients and facilities; in-office procedures lessen staff requirements, resource consumption and hospitalizations, while maintaining positive morbidity and cosmesis outcomes.[2]

This innovation is especially impactful in the geriatric population, where the risks of surgery are complicated by frailties of extreme age and comorbid conditions.[4] Breast cancer is most commonly diagnosed in the sixth and seventh decade. In a study of 120,000 women, recommendations against surgery were primarily due to patients being of senior age.[5] As the brain grows older, it is less resilient to the neurotoxins induced by general anesthesia; accumulation leads to cerebral inflammation and postoperative cognitive dysfunction.[6] Additionally, elderly patients are at greater risk of acquiring hospital borne illnesses following surgery, including pneumonia, urinary infections and pressure injuries.[7] The above elements frequently lead physicians to offer systemic-only treatment for these patients. However, the value of local excision cannot be overlooked; its omission from the treatment algorithm is proven to lead to poorer outcomes, reinforcing the necessity for minimally invasive interventions.[5]

Advancements in breast cancer genomics and accumulation of experience with thermal ablation have identified a favorable subset of patients to undergo this treatment modality; those most likely to benefit are diagnosed with early-stage invasive ductal carcinoma (IDCA) measuring less than 2 cm in diameter, and whose tumor biology is hormone receptor positive and HER2 negative.[8] Cancer cells with one or both estrogen (ER) or progesterone (PR) receptors are characterized as “hormone-positive”; human epidermal growth factor receptor 2 (HER2) is a protein that helps cancer cells grow quickly: breast tumors with higher-than-normal levels of

HER2 are characterized as “HER2 positive”.[3] Furthermore, thermal ablation is most appropriate in addressing a single foci of tumor due to the highly localized nature of treatment probes. Women with multifocal cancer, meaning the breast is inflicted with two or more distinct tumors, require more extensive local treatment. Similarly, tumors classified as having an extensive intraductal component (EIC) are also excluded. EIC is a term describing a unique form of cancer which spreads diffusely throughout the breast; this is considered a significant risk factor for local recurrence.[9] All studies reviewed here utilize a benchmark of excluding tumors with EIC greater than 25%. In the instance of multifocality or EIC, a mastectomy is most appropriate. Regardless of intervention, adjuvant therapy is standard of care; this includes chemotherapy, radiation, hormone and endocrine therapy.[8] The course and combination of ancillary treatment is a shared patient-provider decision, personalized to the patient’s age, specific tumor biology, the extent of spread and other intricate factors.

A limitation of thermal ablation to this point is determining if complete tumor eradication is achieved. Margin status is one of the most important factors influencing long term outcomes, regardless of malignancy type.[10] During a lumpectomy, sections of the surgical bed and tissue surrounding the excisional site are sent to pathology for intraoperative evaluation, where the presence of residual tumor may or may not be identified[11] In the case of a positive margin, more tissue will be excised by the surgeon until a negative result is achieved. Following surgery, standard pathological evaluation ensues. This process involves formalin fixation and embedding any removed tissue in paraffin wax, from which slides are prepared, and stained with standard hematoxylin and eosin (H&E). The H&E dye highlights cellular structures allowing the pathologist to identify the presence of residual tumor.[12] This confirmatory practice is not yet established in the case of thermal ablation. First, removing margins of tissue requires general

anesthesia, which defeats the purpose of a minimally invasive in-office procedure.[10] Second, when margins are obtained, it is debated how to determine if cell death has occurred following treatment; each ablative modality uniquely impacts the microcellular environment with the added complexity of having a time-dependent effect.[12] Third, imaging is unreliable in identifying residual cancer following ablation, as well as detecting recurrence on follow-up scans.[3]

As detailed above, significant obstacles withstand the entry of thermal ablation into routine clinical practice. However, for elderly patients who are poor surgical candidates or whose preference is for minimal invasion, further understanding of its application is warranted. Owing to the infancy of this treatment modality, not one standardized evaluation protocol exists. Therefore, any effort to construct a meaningful conclusion in regards to thermal ablation's efficacy requires drawing from an eclectic pool of evidence. In the following literature review, efficacy is assessed through several different means: margin involvement, biopsy, imaging, rate of tumor recurrence and overall patient survival. The aim of the present analysis is to examine if thermal ablation possesses a superior efficacy to that of conventional surgical intervention in the treatment of IDCA. These results will be further explored in the setting of geriatrics as either having legitimate application or if current treatment standards should be maintained.

Methods

A comprehensive literature review was conducted using the Augsburg University Lindell Library database, Google Scholar, PubMed, ScienceDirect and Wiley Online Library. *Key search terms or phrases* included breast cancer, percutaneous thermal ablation, cryoablation, radiofrequency ablation, high-intensity focused ultrasound, microwave ablation, laser ablation, histopathology, margin evaluation and geriatric. Primary research and controlled trials were

utilized for analysis, and reviews as supportive evidence; animal studies were not considered. The *major study inclusion criteria* were as follows: studies published in or after 2015 using thermal ablation as principal intervention of primary breast cancer. A *secondary inclusion criterion* was a focus on patients diagnosed with IDCA; it was not grounds for exclusion if studies also included a minor patient pool with ductal carcinoma in situ (DCIS). While few studies included patients with metastasis, the majority focused on patients with a singular breast tumor without evidence of spread. A *tertiary inclusion criterion* was demonstration of conditional post-procedural follow-up, such as surgical margin evaluation, imaging (ultrasound, mammography, MRI, CT, PET scan) or needle core biopsy in addition to physical examination. The *major study exclusion criteria* ruled out studies published in or before 2014, providing patients neoadjuvant therapy, using thermal ablation to treat secondary metastatic lesions in the breast or a primary focus on patients with metastatic breast cancer.

Review of Literature

To reiterate, the following are the most prominent thermal ablation procedures for the treatment of IDCA: cryoablation, radiofrequency ablation (RFA), laser ablation (LA), microwave ablation (MWA) and high-intensity forced ultrasound (HIFU). Cryoablation and RFA have the longest studied histories, and hence, possess the most evidence of their efficacy; therefore, each will be the focus of an independent section. More recently, successful applications of LA, MWA and HIFU have been reported. Due to the smaller body of evidence, these techniques will be the focus of a combined third section.

Furthermore, a commonality amongst all thermal ablation procedures is the use of image guidance for placing and monitoring probe position. By far, ultrasound endures as the top choice

of providers, though computed tomography scan (CT) and magnetic resonance imaging (MRI) have also demonstrated utility. Image guidance allows providers to see their ablation tool in relation to the tumor throughout the procedure. Additionally, thermal-induced damage of tissue can be visualized in real-time, ensuring complete ablation is grossly achieved[10]

Below, a technical discussion of the ablation modality will be presented, followed by a discussion of the current literature.

Part I: Cryoablation

As its name implies, cryoablation utilizes extreme cold to obliterate a tumor volume. This modality has been successfully used for decades to treat various diseases in multiple organ systems; most notably these include the lungs, liver, kidneys and prostate.[4] Its initial application in breast tissue was to treat fibroadenomas, until the late 1980s when its use expanded to cancer.[4] Cryoablation is an office-based procedure performed with local anesthetic, allowing patients to stay awake. The cryoablation probe is inserted through a small incision made in the skin. Over the course of 30-minutes, liquid nitrogen or argon gas is pumped into the cryoprobe. The site is frozen (target temperature < -40°C), allowed to thaw, and then is frozen again.[13] The goal is to encase the tumor in ice, plus a circumferential margin of several millimeters; this process is visualized on imaging and indicates the procedure was grossly successful.[13] The most optimal results are achieved when multiple probes are activated simultaneously with synergistic effects.[14]

This series of freeze-thaw-freeze cycles leads to osmotic dehydration of tumor cells, resulting in necrosis and apoptosis. These processes trigger the immune system to continue mounting an attack on malignant cells in the weeks following cryoablation.[8,13,15] A “stone-like” consistency is palpable for 3-12 months along the zone of ablation, which resolves without

changing the breast's appearance.[14] A notable strength of this modality is that post-operatively, the hypothermic temperatures act as an intrinsic analgesic.[16] Patients report minimal to no discomfort in the days to weeks following treatment, and complications are rarely reported.

Studies

The Z1072 trial powered by the American College of Surgeons Oncology Group (ACSOG) investigated the efficacy of cryoablation as primary treatment for IDCA.[9] Between 2009 and 2013, 86-patients underwent cryoablation followed by margin excision within a period of 28 days; this method is termed the "treat-and-resect" protocol. ACSOG sought to determine the rate of complete tumor ablation, defined as an absence of residual disease on pathological examination. Margins were analyzed by an institutional pathologist, and then sent for central review. The inclusion criteria for this study reflects the ideal candidate for thermal ablation: patients with unifocal IDCA < 2cm in diameter and < 25% EIC. One patient had a singular tumor in bilateral breasts, increasing the number of tumors assessed to 87. The mean patient age and tumor size was 62 years and 1.2 cm, respectively.[9]

Z1072 demonstrates the effectiveness of cryoablation, while also highlighting a significant gap in its advancement. In 84-cases, over 19 independent institutions, providers successfully operated the device – speaking to its clinical adaptability; gross misplacement of the cryoprobe was only seen in 2-cases[9]. Following double pathological evaluation, 66 of 87 (75.9%) tumors were completely ablated, while 4 were partially ablated. Authors suggest in the latter, that tumor size may have been initially underestimated on imaging or had poor demarcation, leading to incomplete ablation. In 15-patients, post-ablation MRI revealed successful ablation of the primary tumor; however, it also identified new tumor foci >2cm outside of this zone. ACSOG

states these cases should not be considered an ablation failure. Notably, excluding this group from study increases the complete tumor ablation rate from 75.9% to 92% (80 of 87 target lesions). Astonishingly, authors report residual foci are commonly found outside the primary tumor site in patients treated with breast conserving therapy.[9] Therefore, while cryoablation is effective at producing an adequate killing zone, it is highly dependent on pre-procedural MRI quality and radiologist interpretation; these elements are crucial for adequate patient selection, which greatly impacts the overall efficacy of cryoablation.

An earlier study in 2015 by Poplack et al. used the same treat-and-resect protocol but on a smaller scale.[16] Twenty patients with tumors < 2cm in diameter underwent cryoablation followed by surgical excision 4-6 weeks later. All tissue was evaluated by an institutional pathologist; 10 patients' tissue was sent for a secondary blinded analysis. Histology revealed pathologically distinct zones: central ischemia and coagulative necrosis, surrounded by a region of inflammatory changes and fat necrosis, then finally a peripheral ring of normal fat and fibroglandular tissue. Within this latter zone, residual cancer was found in 3-patients. As in Z1072, this implies the cryoprobe was likely misplaced, rather than ablation failure in the central zone. These patients also shared an initial diagnosis of DCIS, versus IDCA, which literature proves is harder to eradicate with thermal ablation in general due to the non-discrete margination of these tumors.[3] Results of the Poplack et reinforce the effectiveness of cryoablation, especially given blinded review in 50% of patients by a centralized, independent pathologist.[16]

The following studies differ from Z1072 and Poplack et al. in that margins are not utilized to verify efficacy. Therefore, proving the non-inferiority of cryoablation to surgical intervention is challenging. Habrawi et al. is a significantly smaller powered prospective study. 12-women recruited with hormonal positive, HER2 negative IDCA measuring < 1.5 cm in

diameter were treated with cryoablation without subsequent excision; follow-up was scheduled every 6 months with the intent to follow patients for 2 years.[4] At 6 months, 11 of 12 patients presented for post-procedural mammography, ultrasound and MRI with no identifiable cancer. Confirmatory needle biopsy in 4 patients demonstrated fat necrosis in place of viable tumor cells, indicating successful ablation; these results were corroborated on ultrasound and MRI. At 1 year, imaging was negative for 8-patients, and at 2 years, 4 patients were negative for recurrence. Though on a very small scale, Habrawi et al. demonstrated cryoablation was effective in avoiding recurrence of IDCA in at least 4 patients.[4] Yet, the evidence presented here is weakened by lackadaisical, vague follow-up criteria set by the authors. At 1-year, 30% of patients failed to return to the clinic and by 2 years, 66% were lost to follow-up.[4] Lastly, it is not stated if the same patients followed up serially, or if each interval consisted of different patients, weaking the longitudinal value of this study.

The ICE3 trial is an industry sponsored, prospective study that also waived excision following cryoablation.[8] This 2021 paper reflects the 3-year interim analysis of the study's anticipated 5-year span (tentative completion date of 2023). 194-patients were recruited from several institutions to determine the efficacy of a newly developed cryoprobe device. Authors acknowledge that omitting definitive surgical management likely biased physicians towards choosing low-risk elderly participants. The mean patient age and tumor size was 75 years and 0.8 cm, respectively.[8] Additional selection bias is seen in this latter element. As tumor size decreases, treatment effectiveness increases; by narrowing in on the population most likely to see benefit, authors strategically build evidence for their device.

Despite significant bias, results of ICE3 underscore the effectiveness of cryoablation in avoiding ipsilateral breast tumor recurrence (IBTR). At the 3-year interim, 98% (191/194) of

patients were negative for IBTR; the mean time to recurrence in the remaining 2% was 43 months.[8] All patients were treated as outpatients and 76% report returning to full daily activities within 2 days of treatment. In agreement with Habrawi et al., ICE3 authors discuss reabsorption of fat necrosis over time on mammography, indicating successful cryoablation. Since 2019, 10-patients have died due to advanced age and preexisting comorbidities, not related to the device.[8] Though, this dropout rate is expected with an aging participant pool. At the completion of its 5-year study period in 2024, results of ICE3 will further validate the reliability of cryoablation without subsequent excision in select patients.

Cazatto et al. is an earlier study published in 2015, and like ICE3, documents cryoablation without subsequent excision in elderly, non-operable patients; median age is 85 years with a median tumor size of 1.4 cm.[14] Authors delineate a "dual-freezing" and a more aggressive "triple-freezing" protocol, which 10 and 13 patients received respectively. Over the 2-year follow-up period, 1 patient died due to myocardial infarction; of the remaining 22 patients, the local tumor control was 76.9% at 1 year and 9% at 24 months. Similar to Habrawi et al, adherence to follow-up protocol was poor: only 5-patients returned for the 2-year follow-up.[4,14] Therefore, the results of this study require careful interpretation. Yet, on the whole, only 5 patients experienced recurrence, and were successfully re-treated with either another round of cryoablation or adjuvant therapy.[14] These results are in agreement with ICE3,, but on a much smaller scale (n=194 vs n=23, respectively).[4,8,14] Patients grossly unsuitable for surgery are a minority, and therefore the small study size is a limitation of this trial. Taken together, however, these studies prove cryoablation alone is well tolerated by the geriatric population, with relatively high efficacy in controlling local recurrence.

The following study focuses on the predictive value of imaging to detect residual and recurrent cancer following cryoablation, which is essential for its clinical adoption. MRI detects tumor vascularity and is a non-invasive method to assess ablation and adjuvant therapy responses.[15] Machida et al. recruited 2 radiologists (observer 1, observer 2) with 16-years of experience to retrospectively look at 54 cases of patients with breast cancer who underwent cryoablation; charts from 2006-2014 were subject to review.[15] Patients were a mean age of 56 years and diagnosed primarily with hormonal positive, HER2 negative IDCA that measured less than 1 cm (median size 0.89 cm). Preemptively, radiologists reviewed non-participant scans to agree upon what they considered abnormal enhancement. From this point, radiologists were blinded to clinical outcomes and asked to assess MRIs for patients post-cryoablation. Statistical analysis scored interobserver agreement using k values: slight (<0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), or almost perfect (0.8-11.0). Post-ablation MRIs were performed an average of 42 days after treatment.[15] However, the mean time between post-ablation MRI and the start of radiation varied widely, which likely impacted the ablation zone's appearance of imaging.

Both observers agreed, between the first and second post-ablation MRI, the treatment zone shrank ($p < 0.001$).[15] Contrarily, interobserver agreement on enhancement shape and degree of suspicion for residual disease or recurrence was only fair to moderate between MRIs. This k value is considerably low and raises concerns if the results presented here are generalizable. It remains controversial what is considered suspicious enhancement within a treated area; this not only varies between observer 1 and 2, but across the field as well. The predictive value of MRI is a secondary outcome in Simmons et al. and Poplack et al.[9,16] In the latter, the accuracy for predicting treatment success was limited. Three of 18 participants showed residual cancer that

MRI failed to detect, yielding a sensitivity of 0% (0/3).[16] Simmons et al. showed low specificity as well: 20% of cases predicted to be negative on MRI were deemed positive on histological examination.[9] In each of these studies, as well as Machida et al., the negative predictive value of imaging proved to be less than reliable, underscoring its inadequacy to detect residual cancer.

Cryoablation has a longstanding history in the treatment of cancer; however, its reliability to specifically detect breast cancer recurrence is questionable. In the van de Voort et al. 2021 meta-analysis, 37 thermal ablation trials were examined from the last twenty years.[3] Of the 8 cryoablation studies included, the primary reasons given for incomplete ablation was multi-focality detected on histologic evaluation and tumor size underestimation on pre-treatment imaging. Each of these inconsistencies are highlighted by the Z1072 trial above.[3] The development and implementation of more sensitive imaging will hurdle cryoablation into the conversation of supplanting lumpectomy as standard of care. The combined analgesic effect of cryoablation, with its moderate to high ablation efficacy, sustains this modality as a hopeful option for elderly, non-surgical candidates.

Part II: RFA

RFA utilizes hyperthermic temperatures to obliterate tumor volume and is considered by many in the field as the most promising of all ablative techniques. Already, it is a mainstay in the treatment of hepatocellular and renal cell carcinoma, and commonly used in coronary catheter ablation for atrial fibrillation.[17] RFA was first used to treat breast cancer in the early 2000s. Yet, general anesthesia continues to be required to withstand its high temperatures – defeating the purpose of being a minimally invasive procedure.

Under ultrasound-guidance, an electrode is advanced through a small skin incision into the center of the tumor; echogenicity resulting from microbubble formation confirms proper placement of the probe.[12] Over the course of 45-minutes, an alternating electric current generates ionic agitation, resulting in localized frictional tissue heating.[18] When the site exceeds > 70°C, protein denaturation occurs, followed by an ellipsoid region of necrosis. At this heat index, the balance of temperature, therapeutic gain and adverse effects is a delicate practice: below the threshold, tumor will not be adequately ablated, but excessive heat can lead to internal charring and skin burns. Charring should be especially avoided as it acts as a very effective insulator, disrupting homogenous heat distribution.[19] A system of chilled water circulates beside the electrode to minimize these issues.[12] Once the tumor and an added margin of safety appear completely hyperechoic on ultrasound, the procedure is considered grossly successful. Lastly, "track ablation mode" is performed, where the pathway through which the electrode was advanced is also ablated. This prevents tumor seeding and achieves complete hemostasis.[10] Like cryoablation, RFA does not leave a lasting impact on the breast's silhouette, but the ablation zone is palpable for several months.[14]

Real-time control and fine adjustment of treatment settings is pivotal to creating an ablation volume of optimal shape and size.[20] Most commonly, a super fine thermocouple-needle system is inserted alongside the electrode into the tumor site. This form of thermometry is considered invasive. These devices can only take single-point, often corrupt measurements, due to their sensitivity to patient breathing, nearby vasculature, cardiac and bowel motion.[19,21] Non-invasive infrared thermometry can be used in addition to the thermocouple-needle system, though it is far less accurate.[19] The development of thermometry devices less susceptible to artifacts during ablation is an area of copious investigation.[20]

A challenge unique to hyperthermic ablation is the process of maintaining a homogenous temperature zone. Heat dispersal is markedly influenced by proximity to major blood vessels; therefore, multiple electrodes placed closely together are required to offset heat loss due to perfusion. If a tumor is near the chest wall or axillary region, this convective cooling effect is especially challenging, as significant vasculature runs in these regions.[19] In such cases, the ablation margin can become unpredictable.

Lastly, it must be noted that cell death due to heat is time dependent.[12] The cell-dying mechanism is the result of vascular thrombosis and gradual failure of the tumor's microcirculation. In the weeks following the procedure, progressive tissue ischemia results in an expanding volume of cell death.[3] Additionally, the immune system is activated by the processes of necrosis and apoptosis, which aids in eradicating residual tumor cells over time.[13] Due to these delayed effects, it is postulated that complete ablation rates increase when the interval between RFA and margin obtainment is prolonged.[3] In studies where margins are harvested immediately following RFA, cell death is likely underestimated. This is a major limitation seen in several studies included for review.

Studies

A retrospective 2018 study reaffirms the importance of patient selection for RFA.[17] Ito et al. analyzed 386 patients across 10 institutions between 2003 and 2009; median patient age and tumor diameter was 54 years and 1.6 cm, respectively.[17] Notably, patients with tumor size of larger than 2 cm in diameter were more likely to experience IBTR than patients with smaller sized tumors ($P<0.001$). Following this trend, IBTR-free survival at 5 years was 97% if a patient's tumor was < 1cm, 94% between 1.1 to 2.0 cm, and 87% in instances of tumor size > 2

cm. Lastly, recurrence following RFA was significantly higher in patients not treated with radiation (18.2%) versus with those undergoing radiation (3.2%; P<0.001).[17] In agreement with the literature to date, Ito et al. establishes RFA as a highly successful procedure in treating tumors < 2 cm in diameter, with the additional recommendation for concurrent radiation.[17]

A monumental 2018 study by Garcia-Tejedor et al. directly compared RFA with immediate surgical excision to lumpectomy alone.[10] Authors hypothesized RFA with excision would reduce intraoperative margin involvement by 30%. Between 2013 and 2017, 40-patients from a single institution were randomized 1:1 to the control (n=20) or study group (n=20); median tumor size was 1.3 and 1.0 cm respectively, with each having an average participant age of 64 years. These values and other baseline characteristics, including menopausal status, tumor grade and molecular subtype, did not differ significantly amongst groups (P>0.05). Tumors were primarily hormone positive, HER2 negative (35/40 total); only 1 patient allocated to the control arm was triple negative (ER/PR negative and HER2 negative). Preoperative needle core biopsies were compared to postoperative margins.[10] Histological evaluation classified surgical margins positivity in two separate ways: first, an intraoperative frozen section stained with Nicotinamide adenine dinucleotide (NADH) diaphorase* turned blue in the presence of viable tumor cells; second, if greater than 10% of the paraffin embedded specimen stained with Cytokeratin 18 (CK18) * turned orange.[12] NADH causes an oxidation reaction in the cytoplasm of viable tumor cells, producing a dark blue stain. This indicates tumor cells are still undergoing respiration (alive), and the test is considered positive. Non-viable tumor cells stain pale gray, indicating they are no longer respiring (dead), and the test is negative.[11] CK18 and CK19 are found in the cytoskeleton of epithelial tumors and are amongst the first proteins broken down in the cell death process, turning the stain from orange to purple. Therefore, these intermediate filament keratins

are markers for apoptosis of tumors. Staining is classified as the percentage of tumor cells with positive staining: less than 10% (negative; purple color), 10%-25%, 26%-50%, 51%-75% and 76%-100% (positive; orange color).[11] Clinical follow up took place 2-weeks after surgery and then every 6-months for the next 2 years.[10]

At histologic evaluation, Garcia-Tejedor et al. observed absence of tumor viability in 80% of patients undergoing RFA plus excision, as opposed to only 45% with standard lumpectomy.[10] Authors detail frozen section results in only 16 of 20 patients in the RFA arm, highlighting the challenge of this particular specimen acquisition. Prior to RFA, all tumors showed NADH positivity, and afterwards, NADH positivity was lost in 13 of 16 tumors (81%), which was considered significant ($P<0.001$). CK18 positivity was present in 19 of 20 cases before RFA, and afterwards was considerably lower in all cases: 8-cases were negative, 11-cases were less than 50% and 1-case showed positive staining ($P<0.001$). Notably, 100% of RFA samples demonstrated a complete absence of staining with either NADH or CK18.[10] Understandably, this detail is absent for the control arm, as staining protocol and interpretation for lumpectomy specimens is standardized across institutions. Despite grouping, adjuvant therapy was sufficient to treat patients with positive margins; no additional surgery was required. At 25 months, no local or systemic recurrences were detected amongst all 40-patients.[10] Though on a moderate scale, the results demonstrated here by Garcia-Tejedor et al. provide baseline evidence establishing RFA as equal or superior to lumpectomy in producing tumor-free margins.[10]

The work published in 2016 by Knuttel et al. underlies the accepted rationalization of margin status seen in Garcia-Tejedor et al. and other studies.[18] Prior to its publication, the

histopathological appearance of ablated tissue was understudied. Knuttel et al. retrospectively assessed cell morphology and viability in 15 women with IDCA < 2.0cm in diameter.[18] The histological material was acquired previously by independent studies in 2014.[18] Patients of the aforementioned studies underwent RFA followed by immediate mastectomy or local excision; specimens were processed with standard H&E staining. Slides containing thermal lesions showed distinct cellular distortion. This includes hyper-eosinophilic stroma and severely elongated nuclei, especially around the probe insertion site. In their discussion, Knuttel et al. refers to a trial that examined histopathological findings of tumors resected 91 days following RFA.[18] Specimens from the latter showed remarkably more degenerative changes than those in Knuttel et al.[18] Taken together, these studies further clarify the interpretation of tumor viability through time, verifying the long-term effects of RFA.

A recent 2021 study further investigates how to reliably assess histological features post-ablation.[12] Guma et al. correlates NADH staining of frozen sections to CK18 and CK19 immunostaining of paraffin-embedded tissue.[12] Twenty women from a single institution diagnosed with IDCA, underwent RFA with immediate surgical excision from 2013 to 2017; average patient age and tumor size was 64 years and 1.1 cm, respectively. In agreement with Knuttel et al., authors describe post-ablative degenerative changes with eosinophilic cytoplasm and streaming nuclei, while the peripheral zone containing healthy tissue showed no change.[12,18] Frozen section staining revealed the following: 13 out of 16 patients (81%) were negative for NADH; in 4 instances, frozen sections could not be obtained due to technical difficulties. Prior to RFA, needle core biopsies were diffusely positive for CK18 and 19. Contrarily, post-RFA, 8-patients were negative for CK18 and CK19, 5 showed less than 10% staining, 6 showed 10-25% staining and one case was positive with 22.5% staining; 98% of tumors were CK18 and CK19

negative or markedly reduced. A Cronbach alpha score of 0.8 indicates a strong correlation amongst the various stains.[12] This internal consistency is significant because when an intraoperative section is not feasible, CK18 and CK19 can be used reliably in place of NADH.[12] Given this evidence, authors claim that by moving away from dependance on frozen sections, surgery will not be required for tumor viability confirmation. Due to its simplicity and reproducibility, immunostaining is highly generalizable, more reliable and cheaper than its intraoperative counterpart.[12]

The data presented above establishes RFA as a promising alternative to breast conserving surgery for patients diagnosed with IDCA measuring < 2 cm. As histological interpretation standardizes, it is more likely RFA will transform to an in-office procedure. In the van de Voort et al. 2021 meta-analysis, 89% (601/652) of tumors treated with RFA were completely ablated. In comparison, only 80% (339/397) of patients undergoing cryoablation had a complete response; these values varied significantly ($P<0.001$). Comprehensive analysis by van de Voort further establishes RFA as having increased efficacy over cryoablation, with the added reassurance that long term outcomes are not jeopardized.[3]

Part III: LA, MWA & HIFU

The following three mechanisms are newer to study in the field of breast cancer treatment, and like RFA, utilize hyperthermia to ablate tumor cells. While each modality employs a unique mechanism of heat production, the same processes of cellular necrosis and delayed cell death described in RFA apply here. Additionally, it should be noted the major issues encountered in RFA are also seen in studies of LA, MWA and HIFU. To reiterate, heat loss as a

result of perfusion with major blood vessels leads to an uneven temperature distribution.[19] Secondly, invasive thermometry is highly susceptible to artifact, however non-invasive thermometry devices are less accurate than their counterparts.[20] Cosmetically, LA, MWA and HIFU produce excellent outcomes, and overall, little patient discomfort is reported. Below, each technique is described in technical detail, followed by a review of the current literature.

A. LA

LA shares the most in common with RFA, however, it can be performed under local anesthetic. Additionally, it is considered to be more accurate and safer near critical structures than other modalities; hence, it is a mainstay of brain surgery.[19] The laser fiber is guided by ultrasound into the center of the tumor, consecutive illuminations are performed between 800 and 3600J (target temperature > 60°C), and then the treatment is completed with track-ablation.[5] Procedure time is approximately 30-minutes and is considered grossly successful when the gas formed during the ablation engulfs the tumor on ultrasound.[5] Fluoroptic thermal probes are inserted to monitor temperature by measuring how fast the emitted light decays.[22,23] As with RFA, charring is counteracted by a saline flow system situated alongside the laser fiber, and a coolant spray is used to prevent skin burns.[5]

Studies

The Phase 2 Open-Label Trial performed in 2018 by Schwartzberg et al. is an industry sponsored analysis of Novilase Laser Therapy system to treat IDCA.[22] The chosen patient study was extremely selective, excluding those with morbid obesity, renal insufficiency or comorbidities impacting life expectancy. Additional exclusion criteria were anything preventing

a patient from undergoing MRI, such as possessing a cardiac pacemaker or metallic implant. Between 2012 to 2015, laser ablation was performed in 61-patients; four weeks later, subjects underwent post-ablation MRI, followed by subsequent surgical excision; average age and tumor diameter was 64 years and 1.1 cm, respectively. Tumors were primarily hormonal positive, HER2 negative (50/61). Complete tumor ablation was observed in 84% of cases (51/61). Post-ablation MRI showed a negative predictive value of 92%, yet it failed to detect residual cancer in 64% of positive cases.[22] Such a low rate of sensitivity weakens evidence for MRI to reliably assess tumor viability. Authors claim imaging and pathology findings are strongly correlated; however, their data suggests otherwise.[22]

In blatant contrast, Nori et al. is a retrospective 2018 study focusing on patients with unresectable IDCA.[5] Twelve elderly women with an average age and tumor size of 79 years and 1.2 cm, respectively, comprised the study population. MRI represents the most sensitive technique to visualize a tumor, however baseline imaging was not feasible in most patients due to severe comorbidities, including but not limited to: diabetes with end stage renal disease, Parkinson's and heart failure. Authors claim this represents a limitation of their study; yet, alternatively, these restrictions actually enhance the merit of their conclusions, as they are typical of this patient population. Complete ablation was grossly visualized on ultrasound for 100% of patients, no serious complications of skin burn or infection occurred and all patients were discharged the same day of treatment. Over 28 months, no patients demonstrated recurrence on follow-up.[5] In line with the fundamental purpose of minimally invasive ablative treatment, the study population of Nori et al. is far more representative than Schwartzberg et al.[5,22]

B. MWA

MWA is capable of ablating larger volumes of tumor and achieving higher intratumoral temperatures than other modalities.[2] Currently, microwaves are utilized in oncology to induce full body hyperthermia. This process enhances the therapeutic effects of adjuvant radiation and chemotherapy.[19] MWA is also widely used to ablate thoracic and gastrointestinal tumors.[19] Yet, it remains the most understudied modality in the treatment of IDCA. Energy deposited by MWA disrupts the dipole moment of water molecules, causing them to oscillate, which generates friction and heat (target temperature > 54°C), leading to coagulative necrosis.[24] Under the guidance of ultrasound, the antenna is inserted percutaneously; placement is confirmed when heat-generated echogenicity is detected; when the tumor site appears completely hyperechoic, track-ablation mode is initiated and the procedure is completed.[2] As compared to RFA, MWA allows more energy to be deposited faster and reach lower depths; however, this increases the risk of thermal injury and decreases predictability of the ablation zone.[19]

Study

A 2020 study retrospectively compared the efficacy of the standard nipple sparing mastectomy (NSM) to microwave ablation alone to treat IDCA.[2] Yu et al. analyzed 64-patient cases taking place between 2014 and 2020 at one institution. Unlike studies discussed in previous sections, the NSM (control) and MWA (study) group were grossly imbalanced, with 21 and 43 participants respectively. Additionally, the mean age of MWA patients was 24 years older than those allocated for NSM ($P<0.001$). Other inconsistencies include menopausal status ($P<0.001$) and the number of patients suffering comorbidities ($P<0.001$) in the MWA arm.

However, tumor size was not significantly different with most measuring below 3 cm in diameter (P=0.81).[2]

The clinical advantage of MWA for this particular patient population was evidenced by the decreased operative time, post-operative hospitalization and blood loss, compared to NSM (P<0.001).[2] In agreement with previous studies, the ablation zone shrank rapidly over the first 6 months. Within the study arm, 2-patients experienced recurrence, aged 78 and 94, versus 3-patients in the control; both MWA subjects denied additional treatment, however neither died due to IDCA. Notably, most patients in this arm did not receive adjuvant therapy due to their age, speaking to the effectiveness of MWA treatment over the average follow-up period of 26 months.[2] Lastly, for all patients, the negative predictive value of MRI was 100%, which is consistent with Schwartzberg et al. and other past studies.[2,22] Several more studies are required to support the data presented here.

C. HIFU

HIFU is unique in that it does not require a probe to be inserted through the skin and into the tumor cavity. However, the procedure does require general anesthesia as it is extremely sensitive to patient movement.[25] Patients are positioned prone with their breasts immersed in degassed water, and ultrasonic waves are sent by transducers in successive sweeps across the tumor (target temperature > 50°C).[19,25,26] In the setting of therapeutic ultrasound, the water acts as an acoustic coupling agent, maximizing the contact between the ultrasound transducer and insonated tissue; this generates focal acoustic energy, ablating the tumor.[19,27] Procedure length averages about 1 hour, however can extend up to 2-hours – the longest of all thermal ablative techniques – as sufficient cooling time is needed between sonications.[3] Echogenicity is again

used to monitor the extent of treatment and determine its gross success, while tissue temperature is monitored using non-invasive MR-thermometry.[19,26] Complications and discomfort are minimal, with breast edema being the most common adverse effect.[26]

Studies

Guan and Xu et al. were the first to directly compare HIFU to standard mastectomy.[26] This 2016 study, adopts the treat-and-resect protocol to characterize the impact of HIFU on tumor vascular supply. Fifty patients were randomized 1:1 to HIFU with subsequent resection 1-2 weeks later (study group; n=25) or mastectomy alone (control group; n=25); patients and providers were blinded to group allocation. Patients were diagnosed with IDCA with an average age and tumor size of 48 years and < 5 cm in diameter, respectively; baseline characteristics and tumor pathology did not differ amongst groups significantly ($P>0.05$).[26]

Compared to mastectomy margins, the vascular structure in the HIFU group was thoroughly destroyed.[26] Microthrombi were distributed throughout the capillaries, venules and arterioles. Extensive damage was visualized in the tunica media and cellular margins were blurred, demonstrative of coagulative necrosis. Pathologists also report signs of tumor dissolution. Under electron microscopy, tumor integrity along with viable cell organelles were visualized in the control group. Contrarily, the tumor capillary bed of the study group appeared utterly disintegrated. At 1-year, local recurrence was detected in both groups, however this data is not reported as the follow-up period is ongoing.[26] Yet, these preliminary results prove HIFU can irreversibly disrupt tumor angiogenesis, thereby halting its chaotic proliferation cycle of growth.[26]

In the same year, an industry sponsored study by Merckel et al. aimed to test a newly developed HIFU system.[25] Ten patients reflecting the prime candidate profile for thermal ablation underwent the treat-and-resect protocol; participants were an average age of 54 years, and diagnosed with a hormonally positive, HER2 negative tumor with a mean size of 2.0 cm. Considering the purpose of this trial, several patients' treatments failed due to technical difficulties. In 4 patients, the sonications sent from the device were misaligned and no tissue coagulation occurred; however, in the remaining 6 patients, tumor necrosis was observed as in Guan and Xu et al.[25,26] As this study illustrates, HIFU is in its incipient form. Device development, provider experience and randomized, prospective trials are required for any conclusions to be made regarding this modality's efficacy.[24]

To conclude, LA, MWA and HIFU share the lowest volume of evidence in the treatment of IDCA. Due to the novelty of these modalities, the studies demonstrate a large heterogeneity, compared to cryoablation and RFA. Based on current literature, the most decisive data lies with LA. Its shared treatment profile with that of RFA and successful application by Nori et al. in the elderly, separates this technique’s potential from MWA and HIFU.[5] Yet, in the 2021 meta-analysis by van de Voort, the primary reason for incomplete ablation in any of these three modalities was device malfunction and technical difficulties, owing to the provider learning phase.[3] Both user experience and device development stand in the way of the clinical adoption of LA, MWA and HIFU in the near future.

Discussion

Three things need to be reliably proven for thermal ablation to supplant breast conserving surgery as standard of care for IDCA. Depending on the population being treated, a nuanced interpretation is required in regards to the following: First, the benefits of forgoing surgery must outweigh the risks. Second, the ablation site and surrounding tissue must be confidently deemed cancer free. Third, across a large population of patients, local recurrence must be very minimal, or more preferably, absent. Here, the utility of thermal ablation in the setting of the elderly will be reconciled.

It is without question that surgical excision is historically proven to lower the risk of local cancer recurrence and metastasis, but at what cost? In considering a young or middle-aged patient, choosing between lumpectomy versus a lesser proven procedure poses significantly more debate than those near the end of life. For the geriatric patient, life expectancy prominently impacts decision-making for both themselves, and their attending provider. In general, the impaired ability to recover, fewer available financial resources, possible lack of transportation and presence of comorbidities influence treatment choices. Through this lens, the information presented here on thermal ablation can take on new, more tailored meaning.

As the above discussion already alluded to, thermal ablation procedures decrease hospitalizations, postoperative infections and adverse events, and overall time of recovery for this particular patient population. An example of this is demonstrated in Nori et al.[5] Even in its infancy, laser ablative technology is sufficiently sophisticated to allow same-day, out-patient services. In terms of the elderly, this drastically reduces morbidity and mortality following cancer treatment. Another clear advantage of thermal ablation is mentioned in Yu et al. where blood loss and operative time is significantly improved over surgery.[2] Although this is the only

study to directly acknowledge this benefit, it can be assumed this is a general improvement regardless of ablative modality.

Regarding the second parameter, deciphering the presence of residual cancer following thermal ablation is a clear challenge of this field. Yet, major advances in terms of histology are demonstrated by Garcia-Tejedor et al.[10] Here, they prove a strong correlation amongst stains performed on frozen and paraffin-embedded tissue. This consistency allows immunostaining to be used as a surrogate marker for tumor viability, which is a more generalizable evaluation method across institutions.[10] Therefore, a needle core biopsy, rather than margins obtained in the operating room, can be used to verify efficacy. This constitutes a major step towards moving thermal ablation out of the hospitals and into the clinics.

A bigger challenge in this regard is the reliability of imaging. Cryoablation studies in particular have not produced promising results in terms of imaging sensitivity. In Machida et al., the interobserver agreement was considerably low.[15] To compound these findings, the sensitivity of MRI to detect residual cancer in Poplack et al. and Simmons et al. was also unacceptably low.[9,16] Contrarily, the negative predictive value of MRI was consistently high amongst studies: in Schwartzberg et al. it was 92% and Yu et al. showed a 100% success rate.[2,22] However, as Nori et al. recognizes, MRI is not always possible in the geriatric population.[5] For these patients, pacemakers, renal insufficiency and other factors contraindicate them from undergoing MRI.[5] In this case, the third aspect of local recurrence control becomes the single most important factor.

The ICE3 trial has one of the longest follow-up periods discussed in the present review.[8] At the 3-year interim, 98% of patients (191/194) were negative for IBTR. As mentioned before, significant bias went into patient selection.[8] However, in terms of legitimate clinical practice, the results of ICE3 portray a likely prognosis for patients who are deemed candidates for thermal

ablation.[8] What is more intriguing, will be the final results published in 2023 at the completion of its 5-year study period. Ito et al. is another high-powered study which demonstrated strong longitudinal value of thermal ablation.[17] Here, in patients with tumor size less than 1 cm, IBTR-free survival at 5 years was 97% and 94% up to 2.0 cm.[17] Lastly, Nori et al. corroborated these results by publishing that at 28 months, 0% of their study population (12/12) showed local recurrence.[5] It cannot be overlooked how when applied to a patient in their seventh decade, an additional 2 to 5-years of tumor free survival is significantly more valuable than a patient in their thirties. Using this perspective, the efficacy of thermal ablation escalates.

Throughout this review, the time-dependent effects of hyperthermic ablation have been discussed, and in terms of IBTR, its most pertinent manifestation occurs in the 2016 study by Garcia-Tejedor et al.[10] At histologic evaluation, neither the control or study group demonstrated 100% tumor-free margins. However, regardless of positive margin status, authors go on to say no patients required additional procedures. At 25 months, no local or systemic recurrences occurred for any participant.[10] In the control group, this is directly related to adjuvant therapy. However, in the RFA with subsequent excision group, it may be attributed to one of two factors: either adjuvant therapy, or, late-onset cell death secondary to thermal ablation and immune system activation.[3,10] Most likely, both processes are at work on residual tumor cells. The 2021 meta-analysis by van de Voort et al. noted the thermal ablative studies in which margin resection was delayed showed higher complete ablation rates.[3] Eight studies extracted margins in under 14-days following ablative therapy, and demonstrated an overall complete ablation rate of 67%.[3] In stark contrast, 10-studies which delayed extraction beyond 2-weeks, showed an overall complete ablation rate of 86%. Authors conclude, these results are likely due to delayed onset of cell death.[3]

In theory, given enough time, the late-onset effects of thermal ablation may independently resolve residual cancer – yet this is not standard of care. Adjuvant therapy, regardless of age, is almost always recommended. Therefore, future studies looking at thermal ablation, without subsequent resection, over a long period of time would be beneficial in building evidence for its clinical adoption. Two studies of this nature are currently underway in Japan and the Netherlands. The RAFAELO study is a prospective phase III study taking place across 11 institutions where patients will undergo RFA without surgical excision.[28] Follow-up is planned for 5-years and results will be compared to previous randomized control studies of lumpectomy or partial mastectomy.[28] More interestingly, the THERMAC trial plans to randomize 63 patients 1:1:1 into three treatment arms: cryoablation, RFA and MWA.[29] They intend to prolong the interval between thermal ablation and surgical excision to allow adequate assessment of complete ablation on MRI and pathology. Therefore, authors assert their results will take into account both direct and delayed effects of thermal ablation.[29] In terms of the geriatric population, long-term positive results from these trials should provide sufficient evidence to assure tumor free survival, likely until the end of these patients' lives.

Taken together, the three conditions presented in the introductory paragraph of this discussion have been fulfilled. Amongst the elderly, for several reasons discussed at length, the minimally invasive option reigns superior to that of general anesthesia and hospitalization. Although the determination of cancer-free margins is not absolute, more exposure to thermal ablation across institutions will improve imaging interpretation, and the detection of residual or recurrent cancer; alternatively in place of surgical margins, the more widely reproducible, economical process of immunostaining can be used to determine tumor viability of needle core biopsies. Lastly, the longevity of thermal ablation to control local recurrence is gaining

considerable evidence. As discussed here, several studies demonstrate an IBTR of 2 to 5 years. This proposed time frame transcends expectations for those near end of life, and provides significant opportunity for safe treatment without loss of efficacy.

Conclusion

The purpose of this analysis was to determine the efficacy of thermal ablation as a reasonable alternative to surgical excision in the treatment of IDCA. This research is not only important, but vital to meeting the ever-increasing demand of an aging population and substantial healthcare worker shortages. Habrawi et al. reports that nearly 70% of those diagnosed with breast cancer each year are classified as low-risk and early stage.[4] This sizable population represents an opportunity to build upon the growing volume of preliminary data for thermal ablation.[30]

While several modalities of thermal ablation exist, the most promising are cryoablation and RFA. These techniques show the highest rate of complete tumor ablation and are the most effective in controlling long term local recurrence. A limitation amongst this field of study is the lack of high powered, prospective trials. However, the completion of the ICE3, RAFAELO and THERMAC trials will help fill this void.[28,29] Until this data is published, breast conserving surgery will endure as the standard of care for the majority of patients. Yet, in the special consideration of the elderly, the use of thermal ablation is justifiable in those unsuitable for surgery or wish to pursue a more minimally invasive option. Further research in this field is strongly warranted, as the reduced morbidity, psychosocial and economic impact of these modalities for the geriatric population is undeniable.

References

1. ACS.org. Breast Cancer Statistics | How Common Is Breast Cancer? Accessed June 29, 2022. https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html

2. Yu J, Han Z yu, Li T, et al. Microwave Ablation Versus Nipple Sparing Mastectomy for Breast Cancer ≤5 cm: A Pilot Cohort Study. *Front Oncol*. 2020;10. Accessed June 14, 2022. https://www.frontiersin.org/article/10.3389/fonc.2020.546883

3. van de Voort EMF, Struik GM, Birnie E, Moelker A, Verhoef C, Klem TMAL. Thermal Ablation as an Alternative for Surgical Resection of Small (≤ 2 cm) Breast Cancers: A Meta-Analysis. *Clin Breast Cancer*. 2021;21(6):e715-e730. doi:10.1016/j.clbc.2021.03.004

4. Habrawi Z, Melkus MW, Khan S, et al. Cryoablation: A promising non-operative therapy for low-risk breast cancer. *Am J Surg*. 2021;221(1):127-133. doi:10.1016/j.amjsurg.2020.07.028

5. Nori J, Gill MK, Meattini I, et al. The Evolving Role of Ultrasound Guided Percutaneous Laser Ablation in Elderly Unresectable Breast Cancer Patients: A Feasibility Pilot Study. *BioMed Res Int*. 2018;2018:1-7. doi:10.1155/2018/9141746

6. Cottrell JE, Hartung J. Anesthesia and Cognitive Outcome in Elderly Patients: A Narrative Viewpoint. *J Neurosurg Anesthesiol*. 2020;32(1):9-17. doi:10.1097/ANA.0000000000000640

7. Cunha AIL, Veronese N, de Melo Borges S, Ricci NA. Frailty as a predictor of adverse outcomes in hospitalized older adults: A systematic review and meta-analysis. *Ageing Res Rev*. 2019;56:100960. doi:10.1016/j.arr.2019.100960

8. Fine RE, Gilmore RC, Dietz JR, et al. Cryoablation Without Excision for Low-Risk Early-Stage Breast Cancer: 3-Year Interim Analysis of Ipsilateral Breast Tumor Recurrence in the ICE3 Trial. *Ann Surg Oncol*. 2021;28(10):5525-5534. doi:10.1245/s10434-021-10501-4

9. Simmons RM, Ballman KV, Cox C, et al. A Phase II Trial Exploring the Success of Cryoablation Therapy in the Treatment of Invasive Breast Carcinoma: Results from ACOSOG (Alliance) Z1072. *Ann Surg Oncol*. 2016;23(8):2438-2445. doi:10.1245/s10434-016-5275-3

10. García-Tejedor A, Guma A, Soler T, et al. Radiofrequency Ablation Followed by Surgical Excision versus Lumpectomy for Early Stage Breast Cancer: A Randomized Phase II Clinical Trial. *Radiology*. 2018;289(2):317-324. doi:10.1148/radiol.2018180235

11. Pleijhuis RG, Graafland M, de Vries J, Bart J, de Jong JS, van Dam GM. Obtaining Adequate Surgical Margins in Breast-Conserving Therapy for Patients with Early-Stage Breast Cancer: Current Modalities and Future Directions. *Ann Surg Oncol*. 2009;16(10):2717-2730. doi:10.1245/s10434-009-0609-z

12. Guma A, Soler T, Chappuis CG, et al. Assessment of Tumor Cell Death After Percutaneous Ultrasound– Guided Radiofrequency Ablation of Breast Carcinoma: A Prospective Study. *Arch Breast Cancer*. Published online July 24, 2021:216-225. doi:10.32768/abc.202183216-225

13. Aarts BM, Klompenhouwer EG, Rice SL, et al. Cryoablation and immunotherapy: an overview of evidence on its synergy. *Insights Imaging*. 2019;10:53. doi:10.1186/s13244-019-0727-5

14. Cazzato RL, de Lara CT, Buy X, et al. Single-Centre Experience with Percutaneous Cryoablation of Breast Cancer in 23 Consecutive Non-surgical Patients. *Cardiovasc Intervent Radiol*. 2015;38(5):1237-1243. doi:10.1007/s00270-015-1181-5

15. Machida Y, Shimauchi A, Igarashi T, Fukuma E. MRI Findings After Cryoablation of Primary Breast Cancer Without Surgical Resection. *Acad Radiol*. 2019;26(6):744-751. doi:10.1016/j.acra.2018.07.012

16. Poplack SP, Levine GM, Henry L, et al. A Pilot Study of Ultrasound-Guided Cryoablation of Invasive Ductal Carcinomas up to 15 mm With MRI Follow-Up and Subsequent Surgical Resection. *AJR Am J Roentgenol*. 2015;204(5):1100-1108. doi:10.2214/AJR.13.12325

17. Ito T, Oura S, Nagamine S, et al. Radiofrequency Ablation of Breast Cancer: A Retrospective Study. *Clin Breast Cancer*. 2018;18(4):e495-e500. doi:10.1016/j.clbc.2017.09.007

18. Knuttel FM, van den Bosch MAAJ, Young-Afat DA, et al. Patient Preferences for Minimally Invasive and Open Locoregional Treatment for Early-Stage Breast Cancer. *Value Health*. 2017;20(3):474-480. doi:10.1016/j.jval.2016.10.013

19. Kok HP, Cressman ENK, Ceelen W, et al. Heating technology for malignant tumors: a review. *Int J Hyperthermia*. 2020;37(1):711-741. doi:10.1080/02656736.2020.1779357

20. Saccomandi P, Frauenfelder G, Massaroni C, et al. Temperature monitoring during radiofrequency ablation of liver: in vivo trials. *Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Int Conf*. 2016;2016:344-347. doi:10.1109/EMBC.2016.7590710

21. Ishizaka H, Shiraishi A, Awata S, Shimizu A, Hirasawa S. Development of a fine thermocouple-needle system for real-time feedback of thermal tumour ablation margin. *Br J Radiol*. 2011;84(1008):1139-1141. doi:10.1259/bjr/81796498

22. Schwartzberg B, Lewin J, Abdelatif O, et al. Phase 2 Open-Label Trial Investigating Percutaneous Laser Ablation for Treatment of Early-Stage Breast Cancer: MRI, Pathology, and Outcome Correlations. *Ann Surg Oncol*. 2018;25(10):2958-2964. doi:10.1245/s10434-018-6623-2

23. Schena E, Saccomandi P, Fong Y. Laser Ablation for Cancer: Past, Present and Future. *J Funct Biomater*. 2017;8(2):19. doi:10.3390/jfb8020019

24. Gala KB, Shetty NS, Patel P, Kulkarni SS. Microwave ablation: How we do it? *Indian J Radiol Imaging*. 2020;30(2):206-213. doi:10.4103/ijri.IJRI_240_19

25. Merckel LG, Knuttel FM, Deckers R, et al. First clinical experience with a dedicated MRI-guided high-intensity focused ultrasound system for breast cancer ablation. *Eur Radiol*. 2016;26(11):4037-4046. doi:10.1007/s00330-016-4222-9

26. Guan L, Xu G. Damage effect of high-intensity focused ultrasound on breast cancer tissues and their vascularities. *World J Surg Oncol*. 2016;14(1):153. doi:10.1186/s12957-016-0908-3

27. Poltawski L, Watson T. Relative transmissivity of ultrasound coupling agents commonly used by therapists in the UK. *Ultrasound Med Biol*. 2007;33(1):120-128. doi:10.1016/j.ultrasmedbio.2006.07.026

28. Kinoshita T. Multicenter Study to Standardize and Evaluate the Efficacy of Radiofrequency Ablation Therapy for Early Breast Cancer (RAFAELO Study). *J Am Coll Surg*. 2019;229(4):e6-e7. doi:10.1016/j.jamcollsurg.2019.08.881

29. van de Voort EMF, Struik GM, Koppert LB, et al. Treatment of early-stage breast cancer with percutaneous thermal ablation, an open-label randomised phase 2 screening trial: rationale and design of the THERMAC trial. *BMJ Open*. 2021;11(9):e052992. doi:10.1136/bmjopen-2021-052992

30. Holmes DR. Breast cancer care during a pandemic: an opportune time for cryoablation? *Breast Cancer Res Treat*. 2020;182(3):515-521. doi:10.1007/s10549-020-05724-0

Appendix

A: *Matrix of included studies*

Acronyms: cytokeratin 18 (CK18), ductal carcinoma in situ (DCIS), extensive intraductal component (EIC), high intensity focused ultrasound (HIFU), invasive ductal carcinoma (IDCA), laser ablation (LA), magnetic resonance imaging (MRI), microwave ablation (MWA), nicotinamide adenine dinucleotide (NADH)radiofrequency ablation (RFA)

REFERENCE & PURPOSE			SOURCES			DATA	VARIABLES		CONCLUSION
Article Title Primary Author	**Year Published**	**Ablation Modality & Purpose**	**Study Size (*n*)**	**Inclusion/ Exclusion Criteria**	**Sample Design**	**Year Data Collected**	**Control**	**Intervention**	
A Pilot Study of Ultrasound-Guided Cryoablation of Invasive Ductal Carcinomas up to 15mm with MRI Follow-Up and Subsequent Surgical Resection Poplack et al.	2015	Cryoablation Evaluate cryoablation efficacy and predictive value of MRI in detecting residual tumor or recurrence	20	IDCA or DCIS Unifocal Tumor size <15mm EIC < 25% Metastasis	Prospective Single arm 2 institutions	Not reported	Not applicable	Cryoablation followed by surgical excision 4-6 weeks later	Authors conclude RFA is effective at local tumor control in patients with tumor size below 2 cm. MRI shows poor correlation with histology following cryoablation.
Single-Centre Experience with Percutaneous Cryoablation of Breast Cancer in 23 Consecutive Non-surgical Patients Cazzato et al.	2015	Cryoablation Evaluation of efficacy in non-operable patients; focus on elderly population	23	Ineligible or denied surgery Unifocal Negative metastasis Metastasis	Prospective Single arm 1 institution	01/2013 - 01/2015	Not applicable	Cryoablation	Cryoablation is an effective means to local tumor control. Authors discuss procedural steps in detail.
Histopathology of Breast Cancer After MRI-Guided High-Intensity Focused Ultrasound and RFA Knuttel et al.	2016	RFA HIFU Evaluate margin status following treatment with RFA or HIFU, followed by surgical excision	25	IDCA Tumor size 1 - 2.0 cm Not reported	Prospective staining Historic specimen acquisition Two arms 1 institution	Not reported	Not applicable	(1) RFA followed by immediate surgical excision (2) HIFU followed by surgical excision 4-6 days later	Cell morphology is uniquely impacted by each technique. Assessment of treatment effect is likely impacted by delayed effects of heat on tumor cells, which possibly underestimates effectiveness of thermal therapies.
A Phase II Trial Exploring the Success of Cryoablation Therapy in the Treatment of Invasive Breast Carcinoma. Results from ACOSOG (Alliance) Z1072 Simmons et al.	2016	Cryoablation Evaluation of complete tumor ablation rate and predictive value of MRI	86	IDCA or DCIS Unifocal Tumor size < 2cm EIC < 25% Lobular carcinoma	Prospective Single arm 19 institutions	03/2009 - 06/2013	Not applicable	Cryoablation followed by MRI within 14-28 days and surgical excision within 28 days	Cryoablation effectively treated 92% of unifocal tumors. Several tumors were determined to be multifocal at follow-up MRI. Post-ablation MRI showed a negative predictive value of 81%.
First Clinical Experience with a Dedicated MRI-Guided High-Intensity Focused Ultrasound Merckel et al.	2016	HIFU Determining the safety profile of a new transducer (industry sponsored)	10	IDCA Tumor size > 1cm	Prospective Single arm 1 institution	09/2012 - 06/2014	Not applicable	HIFU followed by surgical excision 48h to 10 days later	Multiple factors were identified as having a negative impact on HIFU efficacy, including breathing patterns and location of tumor in relation to the chest wall and vasculature.
Damage Effect of High-Intensity Focused Ultrasound on Breast Cancer Tissues and their Vascularities Guan & Xu et al.	2016	HIFU Evaluation of HIFU on tumor vasculature	50	IDCA Tumor size < 5cm Unifocal	Prospective Two arms 1 institution	02/2014 - 08/2014	Radical mastectomy	HIFU followed by modified radical mastectomy 1-2 weeks later	Thermal ablation showed considerable impact on tumor vasculature while leaving healthy breast tissue intact.
Phase II Open-Label Trial Investigating Percutaneous Laser Ablation for Treatment of Early-Stage Breast Cancer: MRI, Pathology, and Outcome Correlations Schwartzberg et al.	2018	LA Evaluation of the efficacy and safety profile of a new transducer (industry sponsored)	61	IDCA or DCIS Tumor size < 20mm Multifocal	Prospective Single arm	06/2012 - 05/2015	Not applicable	Laser ablation followed by surgical excision within 28 days	Histology confirmed loss of post-ablation cell viability. Authors comment on technical aspects of the procedure/

REFERENCE & PURPOSE			SOURCES			DATA	VARIABLES		CONCLUSION
Article Title Primary Author	**Year Published**	**Ablation Modality & Purpose**	**Study Size (*n*)**	**Inclusion/ Exclusion Criteria**	**Sample Design**	**Year Data Collected**	**Control**	**Intervention**	
Radiofrequency Ablation of Breast Cancer: A Retrospective Study Ito et al.	2018	RFA Evaluation of RFA as stand-alone therapy or in concert with radiation	386	Tumor size < 3.5cm Multifocal	Retrospective Single arm 10 institutions	07/2003 - 06/2009	Not applicable	RFA	RFA should not be offered to patients without also performing radiation therapy. Local recurrence rate without irradiation versus those with irradiation (p<0.001).
Radiofrequency Ablation Followed by Surgical excision Versus Lumpectomy for Early-Stage Breast Cancer: A Randomized Phase II Clinical Trial García-Tejedor et al.	2018	RFA Evaluation of RFA with surgical excision versus lumpectomy alone	40	IDCA Tumor size < 20cm < 20% EIC Her2 negative Neoadjuvant therapy Lobular carcinoma	Prospective Two arms 1 institution	09/2013 - 02/2017	Lumpectomy	RFA followed by immediate surgical excision	RFA reduced margin involvement more consistently than traditional lumpectomy (p=0.022).
MRI Findings After Cryoablation of Primary Breast Cancer Without Surgical Excision Machida et al.	2019	Cryoablation Evaluate predictive value of MRI in detecting residual tumor or recurrence	54	IDCA or DCIS Tumor size < 15mm Her2 negative	Retrospective Single arm Not reported	10/2006 - 10/2014	Not applicable	Cryoablation	Suspicious enhancement on 1st MRI status post cryoablation was resolved on 2nd MRI following an additional cryoablation treatment and adjuvant therapy. It is unclear if identified sites were resolved due to cryoablation or adjuvant therapy.
Microwave Ablation Versus Nipple Sparing Mastectomy for Breast Cancer <5 cm: A Pilot Study Yu et al.	2020	MWA Evaluation of local and systemic tumor recurrence in patients treated with MWA therapy alone or lumpectomy	64	IDCA Tumor size < 5cm Multifocal Extensive EIC	Retrospective Two arms 1 institution	10/2014 - 05/2020	Nipple sparing mastectomy	MWA	MWA is as effective as surgical intervention in preventing tumor progression. The MWA study group had significantly more elderly patients with comorbidities compared to the control group.
Cryoablation: A Promising Non-Operative Therapy for Low-Risk Breast Cancer Habrawi et al.	2021	Cryoablation Evaluation of therapeutic efficacy without surgical excision	12	IDCA Tumor size < 1.5mm HER2 negative Unifocal	Prospective Single arm 1 institution	01/2017 - 02/2020	Not applicable	Cryoablation	Cryoablation was effective in preventing recurrent disease throughout the 2-year follow-up period. Small sample size of this study makes proving non-inferiority of cryoablation to surgery hard to prove.
Assessment of Tumor Cell Death After Percutaneous Ultrasound-Guided Radiofrequency Ablation of Breast Carcinoma: A Prospective Study Guma et al.	2021	RFA Evaluate predictive value of different staining techniques in assessing margins for tumor cell viability	20	IDCA Tumor size < 20mm Unifocal Neoadjuvant therapy EIC >20%	Prospective Single arm 1 institution	09/2013 - 02/2017	Not applicable	RFA with immediate surgical resection	CK18 is as effective as NADH in detecting residual tumor viability following RFA. CK18 and CK19 immunohistochemistry is simpler and more economical than methods using frozen tissues.
Cryoablation Without Excision for Low-Risk Early-Stage Breast Cancer: 3-Year Interim Analysis of Ipsilateral Breast Tumor Recurrence in the ICE3 Trial Fine et al.	2021	Cryoablation Evaluation of the efficacy of a new transducer (industry sponsored)	194	IDCA Tumor size < 2cm HER2 negative EIC < 25% Multifocal	Prospective Single arm Multi-center	10/2014 - End date not reported	Not applicable	Cryoablation	The ProSense Cryosurgical System is effective in preventing ipsilateral breast tumor recurrence at 3-year follow-up. Trial follow-up period to continue until 2024 for a total of 5 years.
Thermal Ablation as an Alternative for Surgical Resection of Small (< 2cm) Breast Cancers Van de Voort et al.	2021	Cryoablation, RFA, MWA, HIFU and LA Evaluation of complete ablation rate	Not applicable	Tumor size < 2cm Exclusion if failure to report complete ablation of tumor, ablation performed after surgical excision and review literature	Meta-analysis Multi-center	Studies ranging 2003 - 2018	Not applicable	Not applicable	Review focused on patients with breast cancer tumors <2cm in diameter. Higher complete ablation rates were found in studies performing delayed resection than in studies performing immediate resection. Complete ablation rates were highest with RFA (92%), MWA (87%) and cryoablation (85%).

REFERENCE & PURPOSE			SOURCES			DATA	VARIABLES		CONCLUSION
Article Title Primary Author	**Year Published**	**Ablation Modality & Purpose**	**Study Size (*n*)**	**Inclusion/ Exclusion Criteria**	**Sample Design**	**Year Data Collected**	**Control**	**Intervention**	
Multicenter Study to Standardize and Evaluate the Efficacy of Radiofrequency Ablation Therapy for Early Breast Cancer (RAFAELO Study) Kinoshita et al.	Ongoing	RFA Evaluation of complete ablation rate without surgical excision	372	Ductal carcinoma Tumor size < 1.5cm Unifocal	Prospective Two arms 9 institutions	08/2013 - 11/2017	Lumpectomy or Partial Mastectomy	RFA Patients randomized to study or control groups.	This phase III study intends to demonstrate the non-inferiority of RFA to standard breast conserving treatment in terms of ipsilateral breast tumor recurrence.
Treatment of Early-Stage Breast Cancer with Percutaneous Thermal Ablation, an Open-Label Randomized Phase II Screening Trial: Rationale and Design of the THERMAC Trial Van de Voort et al.	Ongoing	Cryoablation, RFA and MWA Evaluation of complete ablation rate using CK8/18 and H&E staining. Secondary outcome to evaluate predictive value of MRI.	63	IDCA Tumor size < 2cm Unifocal Neoadjuvant therapy EIC > 25%	Prospective Three arms Multi-center	Date of first enrollment: 04/2021 Recruitment Status: Recruiting	Not applicable	Patients randomized 1:1:1 to one of three thermal ablative techniques. Three months later, surgical excision will be performed to determine efficacy. Patients and physicians will not be blinded.	The technique demonstrating the highest tumor ablation rate will be chosen to be studied in a phase III trial comparing it to standard of care (breast conserving surgery).

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