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Review

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Cryotherapy in the Treatment of Early-Stage Breast Cancer

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Abstract

Breast cancer is one of the most common malignancies, affecting millions of people worldwide annually. The treatment paradigm for early-stage breast cancer is in flux. The focus is now on opportunities to de-escalation treatment to minimize morbidity and maximize patients' quality of life. Recently, percutaneous minimally invasive ablative techniques have been explored. Early trials in small population of patients demonstrated cryoablation to be effective, safe, and well-tolerated in an outpatient setting. Subsequent surgical resection was performed and the ablation success rate was the highest if the tumor was less than 1.5 cm and with < 25% ductal carcinoma *in situ* component. ACOSOG Alliance Z1072, a phase II trial with curative intent, demonstrated 100% ablation in all tumors smaller than 1 cm and 92% success in lesions without multifocal disease and less than 2 cm in size. There are ongoing prospective clinical trials to investigate the efficacy of cryoablation without surgical excision for treatment of early-stage breast cancer. FROST (Freezing Instead of Removal Of Small Tumors) started in 2016 is ongoing, ICE3 (Cryoablation of Low Risk Small Breast Cancer) started in 2014 just released 5 years results, and COOL-IT: Cryoablation vs Lumpectomy in T1 Breast Cancers is also ongoing. These prospective trials will expand our knowledge on the safety and value of cryoablation. It is crucial to understand the indications, technical nuances, and distinctive imaging findings for cryoablation as it has potential to revolutionize standard surgical practice.

Keywords: Breast cancer; Cryoablation; Cryobiology; De-escalation

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Introduction

Surgical treatment for breast cancer continues to transform with de-escalation as the driving force [1]. Currently, breast-conserving surgery is the standard of care for early-stage breast cancer with no significant difference in survival rates compared to mastectomy [2]. Several image-guided percutaneous techniques are at the forefront of the de-escalation movement with cryoablation leading the pack. Early-stage breast cancer for this review is defined as stage 1A with T1 tumors and clinically node-negative lymph nodes.

Ablative techniques used in breast cancer are cryoablation, radiofrequency ablation (RFA), microwave ablation (MWA), and high-intensity focused ultrasound (HIFU) [3]. RFA generates radiofrequency waves in an electric circuit that reaches temperatures between 60 and 100 °C. The thermal energy causes directed necrosis. RFA has demonstrated high complete ablation rate in tumors < 2 cm but it has not been consistent. Complications have been mostly technical such as probe positioning or skin burns near grounding pads [4]. The majority of studies included general anesthesia although a few studies have demonstrated safety with local anesthesia. A retrospective analysis involving 386 patients by Ito and colleagues revealed 5-year local recurrence-free survival rates of 97% for patients with tumors less than or equal to 1.0 cm in diameter, 94% for patients with tumors measuring 1.1 - 2.0 cm, and 87% for patients with tumors measuring 2.1 cm or larger. MWA, another hyperthermic technique, is effective in tissues with high water content which may be advantageous to spare the normal fatty breast tissue with lower water content compared to tumor cells. It has been shown to require shorter treatment times, achieve higher intra-tumoral temperatures, and produce a larger area of necrosis compared to RFA [5]. MWA is more painful than other ablative techniques. HIFU is a non-invasive technique that does not require any skin incision. Studies have demonstrated high technical success rates, which provides the opportunity for simultaneous drug injection. Disadvantages include that durations can last several hours, making patient immobilization difficult which affects success [6].

Cryoablation has demonstrated efficacy with low local recurrence rates and is well tolerated in an outpatient setting under local anesthesia alone [7, 8]. It eliminates the need for an operating room and spares the patient the risk of general anesthesia. This makes it an attractive intervention for patients with high-risk comorbidities like pulmonary and cardiovascular disease. The time of the procedure averages less than 45 min compared to several hours for surgical intervention reducing healthcare burden. Furthermore, patients and physicians

have reported great cosmetic outcomes, likely due to volume preservation [9]. It is also important to note that most patients had receptor profiles consistent with luminal A cancers, highlighting the importance of patient selection. The availability of commercial liquefied gases has revolutionized modern cryosurgery, offering novel treatment options [10].

Early Trials in Breast Disease

Cryoablation has been used to treat both benign and malignant breast diseases. Fibroadenomas have been ablated for over a decade [11]. Volume reduction of 89% has been documented and patients have resolution of palpable mass with good cosmesis [12]. This technique has been extended to invasive carcinomas with ablation success rates ranging from 76% to 100% for tumors up to 2 cm in size [7, 8].

In 2004, Sabel et al reported on 27 patients with invasive carcinomas who underwent ultrasound (US)-guided cryoablation followed by surgical resection 1 to 4 weeks later [13]. A tabletop argon gas-based system, Visica, was designed to create probe temperatures of -160 °C. All patients had a double freeze/thaw cycle. During the trial, two different probes were employed, so total cycle times were altered. The first probe was 2.4 mm in diameter and the second was 2.7 mm in diameter but had improved insulation with cooling only occurring at its distal 4 cm. In tumors ≤ 1.0 cm, there was 100% successful ablation. In tumors between 1.0 and 1.5 cm, a 100% success rate was obtained only for tumors without a significant ductal carcinoma *in situ* (DCIS) component. They concluded that cryoablation is best suited for tumors less than 1.5 cm in maximum diameter and having < 25% DCIS component in the core biopsy [13].

Also in 2004, Roubidoux et al reported results of cryoablation in nine patients with small invasive breast carcinomas followed by tumor resection [14]. No residual invasive cancer was found in tumors ≤ 1.7 cm. One patient with a 1.8 cm tumor had a small focus of residual invasive cancer, and one patient had extensive multifocal DCIS not originally detected on imaging [14].

In 2016, ACOSOG Alliance Z1072, a phase II trial investigating cryoablation for early breast cancer with curative intent was published [8]. Eighty-six patients were included with unifocal invasive ductal breast cancer ≤ 2 cm, with less than 25% intraductal component/tumor enhancement on magnetic resonance imaging (MRI). Patients were evaluated with mammogram, US, and MRI. Then cryoablation was completed, and all cryoablations were performed using Visica2 treatment system. Breast MRI was then repeated, and surgical resection was performed within 28 days of cryoablation. The primary endpoint was the rate of complete tumor ablation, defined as no remaining foci of either invasive or DCIS on pathological examination of the targeted lesion. There was no residual invasive carcinoma in 75.9% of cases and 92% success in lesions without multifocal disease and less than 2 cm in size. There was 100% ablation in all tumors smaller than 1 cm. The authors supported cryoablation in highly selected patients and cautioned that multifocal disease may limit the efficacy [8].

More recently in 2023, Roca Navarro et al published their treatment of 20 patients with < 2 cm invasive ductal carcinoma, hormone receptor-positive, human epidermal growth factor 2 (HER2)-negative, who underwent triple (freeze-thaw) phase cryoablation followed by surgical excision (6 - 49 days post-cryoablation) of the tumor and found no residual carcinoma in 19 patients and < 1 mm invasive cancer in one patient [15]. In this study, the cryoablation procedure was performed by a radiologist with a Sentimag magnetic seed marker placement followed by a 17-G or 14-G ICEfX cryoablation needle by Boston Scientific-Galil inserted through the same point with argon gas, with the guidance of US throughout.

It is important to note that due to the multicentric nature of invasive lobular carcinoma and poor imaging correlation to actual extent of disease, these patients have been excluded from most studies [16].

Current Curative Breast Cancer Clinical Trials

Two ongoing prospective clinical trials are investigating the efficacy of cryoablation without surgical excision for treatment of early-stage breast cancer in the USA: FROST (Freezing Instead of Removal Of Small Tumors) started in 2016, and ICE3 (Cryoablation of Low Risk Small Breast Cancer) started in 2014.

The FROST trial included women aged ≥ 50 years with US visible unifocal invasive ductal carcinoma ≤ 1.5 cm in its greatest diameter, estrogen receptor (ER)/progesterone receptor (PR)-positive and HER2-negative, and clinically lymph node-negative. The lesion had to be US visible, with < 25% intraductal component in aggregate, and agreeable to 5 years minimum of endocrine therapy after cryoablation. Patients underwent US-guided cryoablation followed 6 months later by a US-guided core biopsy of the cryoablated lesion to confirm the absence of residual viable disease. Imaging follow-up included serial mammography, US, and MRI. The endpoint of this study is no clinical or imaging evidence of residual or recurrent tumor at 5 years after US cryoablation. If a patient is found to have residual or recurrent disease on follow-up, standard surgical excision is completed. Interim results at 1-year short-term follow-up demonstrated a 1.1% local recurrence rate. There have been no long-term follow-up published to date [17].

The ICE3 trial included women aged ≥ 60 years with US visible unifocal invasive ductal carcinoma ≤ 1.5 cm in its greatest diameter, ER/PR-positive and HER2-negative, a low to intermediate histology grade (Nottingham grade ≤ 2), and clinically lymph node-negative [7]. Patients were excluded if the core biopsy specimen contained 25% or more intraductal neoplasia or if they received neoadjuvant therapy in any form. The endpoint was no clinical or imaging evidence of residual or recurrent tumor at 5 years after US-guided cryoablation. A total of 194 patients with a mean age of 75 years underwent cryoablation treatment in the outpatient setting. All procedures were performed using the ProSense Cyrosurgical System, a liquid nitrogen system that can reach cooling temperatures of -170 °C. The device was inserted with a stab incision and one treatment session with a double-freezing method was used for

each patient with the goal of a 35 - 40 mm ice ball creation. The patients were followed by clinical breast exam and breast imaging at 6 months and then annually at 12, 24, 36, 48, and 60 months after the procedure. Three-year interim analysis results of ICE3 were published in 2021. The mean age was 75 years (range, 55 - 94 years). The mean tumor length was 8.1 mm (range, 8 - 14.9 mm), and the mean tumor width was 7.4 mm (range, 2.8 - 14 mm). These results demonstrated an ipsilateral breast tumor recurrence rate of 2.06% (4/194 patients), similar to that of breast-conserving therapy. There were mild or moderate device-related adverse events in 20.8% of patients. These included bruising, minor skin freeze burn, rash, mild bleeding, pain in needle insertion, and pruritis. Two patients (0.9%) had moderate freeze-related skin burns requiring topical treatment. No severe adverse events or complications were reported. In addition, 95% of patients and 98% of physicians were satisfied with the cosmetic outcome [7]. Preliminary 5-year results of ICE3 demonstrated 96.4% local tumor recurrence-free rate, 7/194 (3.6%) in breast tumor recurrence. At 5 years, 100% of patients and physicians reported satisfactory cosmetic outcomes. Breast cancer survival was 96.7% with five breast cancer deaths, three of which were unknown [18]. The authors concluded that cryoablation is a safe, percutaneous ablative procedure with an acceptably low 5-year recurrence rate. The mean size of tumor was 0.8 cm, making results most applicable to patients with small, hormone-positive breast cancers.

A more recent randomized clinical trial has begun recruiting, COOL-IT: Cryoablation vs Lumpectomy in T1 Breast Cancers. This trial aims to study the efficacy and safety of cryoablation in patients aged 50 years and older with early-stage cancer, less than 2 cm of the luminal type A (ER/PR-positive, HER-2-negative) that is grade 1 or 2 with intraductal component < 25%. Genomics has been incorporated and patients must have an oncotype less than 26. The primary outcome is ipsilateral breast tumor recurrence rate at 5 years [19].

The American Society of Breast Surgeons consensus guideline on the Use of Transcutaneous and Percutaneous Ablation for the Treatment of Benign and Malignant Tumors of the Breast details that at this time, there are no FDA-approved percutaneous or transcutaneous ablative treatments for breast cancer [20].

Cryobiology

Cryoablation requires a freeze cycle, passive thaw, and lastly a second freeze cycle. The exceptionally cold temperatures and ice crystal formation result in deleterious effects by direct and indirect mechanisms, namely osmotic effects, intracellular ice formation, microvascular thrombosis, and apoptosis. Direct cellular injury occurs when freezing causes cellular dehydration [21]. Extracellular ice crystals form first as extracellular water freezes before intracellular water due to the lipid bilayer. The solute concentration outside of the cell is higher which results in fluid leaving the cell. This fluid sequestration results in cell shrinkage and alteration of the plasma membrane. The osmotic gradient is reversed during the passive thaw, resulting in the swelling, and bursting of the cell. This highlights the importance of the passive thaw [3, 22, 23]. In addition to the direct injury from cell dehydration, intracellular crystallization results in mechanical damage due to shearing forces affecting cell membrane integrity and destruction to organelles, enzymes, and proteins [24-26].

Indirect vascular injury also occurs. Micro-circulatory collapse results from cold-induced endothelial damage and vasoconstriction. A cascade of platelet aggregation, vascular stasis and micro-thrombosis unfolds. This results in ischemic death to the targeted area, and this furthers the coagulative necrosis. Furthermore, the increased capillary permeability resulting from the vascular damage results in tissue edema and contributes to the ischemia [21, 25].

Direct cold-induced coagulative necrosis occurs at the center of cryo-ablated lesions, whereas apoptosis has been observed at the periphery [25]. Both intrinsic (mitochondrial-related) and extrinsic (membrane-related) apoptosis have been shown to affect cell death in a cryogenic lesion [24]. The balance between necrosis and apoptosis has implications for the potential immunomodulation due to expulsion of intracellular contents which alerts the innate immune system [21].

The mechanisms of cell death initiated by cryoablation represent a chain reaction, primarily direct injury to the cells caused by ice crystal formation, secondarily malfunction of the microcirculation following thawing, and the induction of apoptosis and necrosis.

Immunological Benefits

Immunomodulation has been suggested as a secondary mechanism of tumor destruction that occurs after cryoablation. This phenomenon involves the generation of an anti-tumor immune response triggered by the natural absorption of the malignant tissue. Other ablative methods use heat which denatures proteins and reduces the amount of intact anti-tumor antigens. Also, heat coagulates tissue preventing the spilling of intracellular products into circulation. With cryoablation, the cells in the center of ablation zone that die by osmotic shock die by necrosis, releasing their intracellular contents into the extracellular space, triggering an active immune response [27]. After cryoablation, pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α, are released in higher quantities than other ablative techniques [28, 29].

One experimental approach for demonstrating an immune response to a tumor was to treat the primary tumor with a first dose, and then, after an interval of time, re-challenge the animal with a second tumor dose. The suppression of tumor growth by secondary dose represents an immune response. Sabel and colleagues demonstrated in a mouse model that the recurrence rate of removed breast cancer was lower after cryoablation compared to surgery (16% vs. 86%) [30]. After cryoablation, levels of IL-12 and interferon (IFN)-gamma in the mice's serum significantly increased which are involved in cell-mediated immunity, and T-cell toxicity in tumor-draining lymph nodes was significantly enhanced. The tumor-infiltrating lymphocytes (TILs) have increased, which has been shown

to indicate better response rates to neoadjuvant chemotherapy and improved survival rates [31].

Misao et al used a murine metastasizing breast adenocarcinoma in rats to compare surgical excision to cryosurgery [32]. Mice were re-inoculated with the same cancer cells after successful local therapy. By week 10, mice treated by cryosurgery had a dramatic improvement in tumor rejection compared to surgery; cryosurgery-treated mice rejected 80% of tumors compared to 18% by surgery. Lymph node metastases were also lower in the cryosurgery-treated group [32]. It is hypothesized that inflammation from cryoablation results in an anti-tumor immune response since the tumor-specific antigens remain *in situ* [31]. If this response could contribute to decreasing local or distant recurrence, it would be the superior method of treatment.

The abscopal effect describes an exceptional occurrence where local treatment of a primary tumor results in tumor regression at distant sites. The immunogenic effects of cryoablation have been described as a possible explanation for this phenomenon. Cryoablation induces the release of inflammatory cytokines and increases natural killer cell activity and tumor-specific T cells, which have been reported to decrease pulmonary metastasis and tumor growth in murine models of breast tumor [33]. Kahn et al recently explored this phenomenon on a mouse model of triple-negative breast cancer. They detected a robust tumor-specific TILs response with cryoablation compared with resection, suggesting an abscopal effect leading to the prevention of cancer recurrence and metastasis [34].

Furthermore, some claim that cryoablation may increase the efficacy of immunotherapy for treatment of breast cancer. However, whether this is the case requires further investigation since some studies have also demonstrated immunosuppressive effects [35].

Technique

The specific technique will be based on tumor size, location, and patient characteristics. Furthermore, the cryogen type and cryoprobe design will determine the temperature, ice ball diameter and cycle times. However, there are a few crucial principles. On a macroscopic view, tissue is frozen rapidly, thawed slowly and completely, and then is exposed to a second freeze cycle. For malignant lesions less than 1 cm, suggested timeframe is 6 min first freeze, 10 min thaw and lastly 6 min of second freeze. For lesions up to 2 cm, the recommended timing is 8 min freeze, 10 min thaw, and 8 min for second freeze [36]. Correct technique accomplishes the goal of achieving a lethal temperature in the target tissues while assuring a safe margin around the tumor. According to experimental studies, efficient cryoablation could be achieved with an 8 - 10 mm margins, some advocating for at least 1 cm visible ice coverage beyond all tumor margins for curative attempt [14, 37]. Repetition of the freeze-thaw cycle subjects the tissues to a repeat and amplification of the injurious events. This double freeze is often considered to be important to ensure proper destruction of malignant tumors. Cancer cell viability sharply decreases with declining temperature, and most cells die as temperatures approach -40 °C [34, 38].

The ICE3 trial used a cryosurgical system that employs liquid nitrogen. The cryoprobe achieves rapid freezing by creating an active freeze zone up to its distal tip. The device achieves rapid and stable cooling alternated with slow thawing that creates an ice ball with large lethal zones. Under US guidance, the cryoprobe is inserted through a stab incision into the center of the lesion along the longest axis of the lesion parallel to the chest wall. Activation of the cryoablation system caused cooling of the cryoprobe to extremely low temperatures of -170 °C. One treatment session with a double-freezing method was used for each patient. The total procedure time was 20 to 40 min [7]. ACOSOG Z1072 trial showed that if the probe is position correctly, there was no viable carcinoma in the cryoablation zone. In some instances, incomplete tumor ablation was due to incorrect placement of the probe [8]. The probe tip should extend 0.5 - 1.0 cm beyond the margin of the mass to ensure a lethal temperature at the margin. A schematic diagram depicting steps of the procedure including preparation, cryoprobe insertion, and peri-operative monitoring can be viewed in Kwong et al [39].

In order to protect the skin, ultrasonography-guided injection of saline between the skin and the ice ball anterior surface was performed if the tumor was less than 0.5 cm from the skin in several studies. The goal was to avoid skin frost injury [7, 8, 26, 40, 41].

Complications/Side Effects

The potential complications of breast cryoablation are similar to those of a core needle breast biopsy and include bleeding, infection, and skin injury [40]. The severity and duration of the cutaneous effects will vary according to the lesion size, lesion location, and depth of freezing. With a skin frost injury, there is edema and erythema that develops immediately along with wound exudate. Postoperative care includes daily cleansing of the wound with soap and water followed by placement of non-adhesive occlusive wound dressings [42, 43]. A common side effect of significant skin frost injury is hypopigmentation as melanocytes are more susceptible than keratinocytes to damage from freezing. Patients should be advised that hypopigmentation may be permanent [42].

In the ICE3 trial, there were minor adverse events such as bruising, minor bleeding, and pain with injection of local anesthetic. Skin burns of a mild to moderate nature were treated without lasting adverse effects. In addition, cosmetic satisfaction was shown to be high (> 95%) among both the patients and the treating physicians [7].

Littrup et al presented a small study of 11 patients and performed saline injections of up to 100 mL for skin protection, allowing the generation of 1-cm ice ablation margins beyond all tumor margins, even if the tumor was within 1 - 2 mm of the skin surface [37]. Bruising and breast edema (grade 1/2) were common for all women but required no drainages or interventions. The average procedure discomfort at 24 h was 0.3 on the 10-point pain scale (range, 0 - 4). The patient with the highest pain score of 4/10 was well controlled with analgesics and had been 3/10 before the procedure due to the subcutaneous/sternal

tumor recurrence. No skin necrosis was noted and no complications of grade 3 or higher were identified [37].

Manenti and colleagues examined cryoablation vs. RFA in 80 women [44]. The absence of skin pigmentation was considered excellent cosmetic outcome (grade 1), slight texture change or mild pigmentation (grade 2), moderate texture change or pigmentation (grade 3), and marked texture or pigmentation changes was poor cosmetic outcome (grade 4). Cosmetic outcome was evaluated immediately after percutaneous ablation and 4 weeks after the procedure. Cryotherapy was determined to provide between cosmesis due to lack of grade 4 outcomes [44].

Imaging After Cryoablation

After cryoablation, clinical and imaging follow-up is needed to confirm successful tumor destruction and monitor recurrent disease. However, currently there is normal formal consensus on the best modality or timeline for post-cryoablation imaging as mammography, US, and MRI each have strengths and shortcomings. Expected post-ablation findings need to be well recognized to be able to distinguish from residual or recurrent cancer.

Imaging at 2 - 3 months after ablation demonstrates early fat necrosis changes at the cryoablation site, presenting as focal asymmetry with internal fat density on mammography and a mass-like area of heterogeneous echogenicity with indistinct margin on sonography. These findings may make it challenging to distinguish residual cancer from post-treatment change [45].

The predominant imaging finding after cryoablation is fat necrosis. The ablation zone can be distinguished immediately after the procedure, but usually post-procedure imaging is not performed for weeks afterward. On US, the residual ablated lesion may still be visible 2 or 3 months after the procedure. By 6 months, sonographic findings will appear typical of fat necrosis, and the residual shape likely will no longer be visible. The ablation zone decreases in size over the following year. Studies have demonstrated that ice is difficult to visualize on mammography. As early as 1 - 2 months after cryoablation, the ablation zone is evident as an area of fat necrosis seen as a rim of white tissue surrounding a mixed-density interior. A marking clip placed at the time of biopsy serves as an important landmark for determining an adequate, well-centered ablation zone [36, 46].

Subtracted contrast-enhanced MRI has demonstrated the ability to demonstrate complete tumor ablation as lack of enhancement in the ablation zone. Studies have found MRI to have a negative predictive value of 81-83% [8]. Post-cryoablation breast MRIs showed avascular ablation areas surrounded by symmetrical peripheral rim enhancement [37, 40, 47]. Suspicious findings for recurrence on MRI include an enhancing mass in the ablation zone, new areas of non-mass enhancement, or nodular enhancement along the periphery of the ablation zone [48].

Machida et al demonstrated the importance of understanding the "new normal" after cryoablation [49]. They examined findings on MRI after cryoablation for breast cancer as determined retrospectively by two independent radiologists. These radiologists identified some suspicious findings within the treated area on the first post-cryoablation (29 - 60 days post-treatment) MRIs on seven of 54 (13.0%) studied patients. All these suspicious findings had resolved by the second post-cryoablation MRI [49]. This suggests that enhancement within treated areas after cryoablation can resolve during subsequent adjuvant therapies and follow-up. Poplack et al supported this notion as they identified central enhancement at the ablation site in two of 17 patients (11.8%); however, residual carcinoma was not found on histopathological analysis of subsequently excised tissue in the two cases [47].

Recently, contrast-enhanced mammography (CEM) has been proposed as a superior imaging modality given its high sensitivity for cancer detection and its advantages in terms of positive predictive value, time, cost, eligibility, and accessibility compared with contrast-enhanced MRI [50]. However, it does require iodine contrast and radiation. The authors recommend a 3-month interval between ablation and the first follow-up imaging examination. Expected findings at this time include a focal asymmetry or mass at the site of the treated lesion within the ablation cavity. By 3 months, the ablation zone has matured and appears as fat density with a high-density rim a so-called cryohalo after cryoablation, that surrounds the ablated lesion [50].

Conclusion

US-guided cryoablation of early-stage breast cancers is a minimally invasive procedure that has demonstrated acceptable local control and good cosmetic outcomes. Further investigation is ongoing to determine the best application of this therapy and appropriate patient selection. Based on current clinical data, ideal patients are those with unifocal small size ($\leq$ 1.5 cm) tumor that is US visible with low histologic grade (Nottingham grade 1-2) and < 25% intraductal carcinoma component or DCIS. Exceptions may be made to include those who are poor surgical candidates or patients who decline surgery. Continued studies regarding post-procedure imaging are needed to determine the best modality to distinguish residual tumor from expected post-ablation changes. Future research is needed to explore cryoablation of the primary tumor in combination with immunotherapy to better understand possible synergy.

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Conflict of Interest

The authors report no conflict of interest relevant to this article.

Author Contributions

CCC was responsible for the conceptualization, development of methodology, literature review and writing of original draft. KT was responsible for conceptualization, writing - review and editing, and supervision.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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