

## Cryoablation of Early-stage Breast Cancer

a report by

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Diagnostic technologies for breast masses have evolved to a point where small lesions are routinely detected. Open surgical biopsies are rarely currently used for the diagnosis of breast abnormalities. Diagnosis and prognosis can be easily assessed by imaging-guided needle biopsy of most of the abnormalities. Along with the advancing diagnostic technology in breast cancer, finding minimally invasive options for the treatment of breast cancer seems to be a natural evolution that has continued since the first described radical mastectomy in the mid 1880s by William Stewart Halsted.<sup>1,2</sup>

### The History of Cryosurgery

Cryosurgery has already been used successfully in treating primary and metastatic liver tumors<sup>3</sup> and prostate cancer.<sup>4</sup> Its efficacy has also been demonstrated in the treatment of ophthalmologic and dermatologic tumors.<sup>5</sup> Historically, Dr James Arnott of the Middlesex Hospital first treated fungated tumors with a mixture of salt and ice, observing reduction of hemorrhage, pain, odor, discharge, and tumor size in 1851.<sup>6</sup> Cryoablation has been known for its use in devitalizing neoplastic lesions for decades.<sup>6-8</sup>

### Cryoablation Today

Recently, cryoablation has been studied as a minimally invasive treatment option for both malignant and benign breast masses. A case of erosive adenomatosis of the nipple was successfully treated by cryosurgery without recurrence after seven years of follow-up.<sup>9</sup> Others have shown that cryoablation is highly successful in treating fibroadenomas and other benign breast lesions.<sup>10-15</sup> In 2001, the Visica™ system for cryoablation of fibroadenomas was approved by the US Food and Drug Administration (FDA).<sup>16,17</sup>

Cryoassisted lumpectomy is another application of this technique for the localization and removal of non-palpable breast lesions. It is also suggested that the chances of clear margins secured by cryo-assisted malignant tumor excision can be significantly improved when compared with the conventional technique.<sup>18</sup>

### The Use of Cryoablation

The major attraction of cryoablation and other *in situ* ablative technologies in the breast are to reduce invasiveness of the surgery and produce good therapeutic effects with more effective cosmetic results.

### Technique and Mechanisms of Cryoablation Damage

Cryoablation of breast cancer consists of localized freezing to destroy tumor cells directly, damaging microcirculation indirectly.<sup>19</sup> The freezing process is generated by a tabletop liquid nitrogen or argon gas-based system designed to create a probe temperature of  $-160^{\circ}\text{C}$ .<sup>13,17,20</sup> A small incision is made after local anesthesia for probe insertion and a cryoprobe is placed in the center of the lesion using the guidance of the ultrasound. The procedure is performed with the patient awake.<sup>10</sup> The cryoprobe is insulated and is directly placed within the tumor (except for the exposed tip).

### Cryoablative Technique

The freezing process starts, creating a visible ice ball from the probe surface outwards,<sup>21</sup> encompassing the tumor on the ultrasound. When the desired amount of tissue has been frozen, the gas flow is stopped and the thaw begins. Cryoablation requires a double freeze-thaw cycle technique to achieve adequate tumor destruction.<sup>22</sup> An injection of saline may be used to increase the distance between the tumor and skin where the two are too close, avoiding hypothermia-induced skin damage.<sup>15</sup> The treated area is left in place to be absorbed by the host inflammatory response.

Magnetic resonance imaging (MRI) was studied as an alternative to the ultrasound that has been used to guide cryoablation.<sup>23-26</sup> However, ultrasound is preferred by most because of its availability and cost-effectiveness.<sup>27</sup>

### Cryoablation and Cell Damage

Many hypotheses have been proposed to explain how cryoablation causes cell damage. The theory is that the concentrated solutes in the extracellular freezing



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area cause cell dehydration, damage to the enzymatic system, and destabilization of the cell membrane. It is also known that the intracellular ice becomes water trapped inside the cell when thawing occurs rapidly. The resulting osmotic disequilibrium causes injury to both the intracellular structures and the membrane. The freezing also induces vessel wall injury, either to its cells directly or to its structure.<sup>28</sup>

Owing to the fact that the cryoablation zone is frozen in place, there is no blood flow into or out of the ice ball. Together, the ischemia and lack of nutrients supply could cause necrosis in the frozen area.<sup>28,29</sup> Hong et al. demonstrated that breast carcinoma cells are more resistant to freezing when compared with normal breast tissue cells. The tightly arranged structure of cancer cells with less extracellular space makes them more resistant to the dehydration process.<sup>30</sup> Their observation supports the proposed extracellular effect of cryoablation on tumor-cell kill.

The freezing damage to breast carcinoma cells increases with decreasing final temperature and accelerated cooling rate. Rui et al. and Rabin et al. reported that two freeze/thaw cycles give better outcome than a single cycle treatment, and the benefit of three or more cycles is minimal, if at all.<sup>19,22</sup>

Another proposed benefit of cryoablation is that it could stimulate an immunologic response, lowering local or systemic tumor recurrence.<sup>31–33</sup> This is based on the fact that the presence of tumor antigens in an inflammatory micro-environment can stimulate anti-tumor immune responses.<sup>34</sup>

Blackwood had already suggested that an immunologic response was motivated by cryoablation although the clinical consequence of this response was uncertain in 1967.<sup>7</sup> Finally, Sabel suggests that cryoablation may be an attractive therapeutic procedure, even if the surgical excision is necessary, as it might reduce cancer recurrence.<sup>31</sup>

### The Advantages and Disadvantages of Cryoablation Use

Some studies included early procedures performed on patients under general anesthesia or in an in-patient setting. With time, it was learned that neither general anesthesia nor intravenous (IV) sedation was required. While the freezing procedure itself generates anesthesia to the breast tissue<sup>29</sup> it allows the procedure to be an office-based modality.<sup>10,15</sup> Cryoablation-induced anesthesia differs from heat-based tissue destruction in that the latter causes enough discomfort to require general anesthesia or significant IV sedation to be provided in an operating room (OR). The need for narcotics for post-operative pain is minimal.<sup>10,20,35</sup>

This procedure is easily followed by ultrasound, because the proximal edge of the ice ball is clearly visible as a hyperechoic rim,<sup>29</sup> which therefore permits skin protection. It should be mentioned that although the ultrasound clearly shows the freezing process the posterior acoustic shadowing prevents imaging of the interior of the ice ball and the area posterior to it, not allowing a precise measurement of the exact size of the ice ball and the distance to the chest wall.<sup>35</sup>

Owing to the fact that the ablated tissues remain in the breast for resorption over time, this procedure has cosmetically acceptable results and does not leave a pronounced scar.<sup>36</sup> Transient and mild ecchymotic changes and post-procedural edema can be seen. Alterations in skin pigmentation, seen in very few cases, is one of the most prominent side effects seen in a long-term follow-up study in patients with benign breast lesions treated with cryoablation.<sup>14</sup> Patchy repigmentation was also observed during the follow-up in goats treated with the cryoablation procedure.<sup>37</sup> Overall, the scarring is considered minimal, the recovery is fast, and patient's self-image is preserved with a high rate of patient satisfaction.<sup>12,14</sup> Due to the fact that the only invasive maneuver is the insertion of the cryoprobe through a 3mm incision in the breast under aseptic technique, the risk of infection is minimal, and there are low rates of treatment-related complications. An important aspect of cryotherapy is that the treatment can be repeated as many times as needed for either recurrences or new lesions, particularly for treating benign lesions.<sup>22</sup> Another advantage of the cryoprocure would be its use to create definite margins in a non-palpable cancer mass that is to be surgically removed. A lower re-excision rate was claimed for carcinomas excised using cryoprocure in comparison with wire localization. It allows the surgeon to dissect around an easily palpable ice ball, facilitating a precise resection of the originally non-palpable tumor. The same study also showed that the cryoablative effect adversely affected a proper determination of nuclear grading, estrogen/progesterone receptors, and HER-2/neu status, but it did not affect the margin evaluation.<sup>18</sup>

### Cryoablation and Breast Cancer

In terms of breast cancer treatment, cryoablation seems to be more effective in invasive cancer than ductal carcinoma *in situ* (DCIS). A tumor size larger than 15–17mm also represents a challenge for complete tumor ablation using the currently available device.<sup>20,35,38</sup> Even at the time when tumor size can be estimated by the available imaging studies,<sup>24,39,40</sup> it may not correspond with the pathologic tumor size. The discrepancy between the clinical and pathologic tumor size can prevent an appropriate tumor ablation.

Some breast cancers, particularly the invasive lobular carcinoma, the malignant microcalcifications, tumors with irregular or ill-defined shape, previous personal history of breast cancer, or other suspicious lesions, should not be considered for cryoablation.<sup>29,41</sup> Sabel et al. suggested that the cryoablation of breast cancer should be restricted to patients with isolated invasive ductal carcinomas up to 1.5cm in size, without an extensive intraductal component in the core needle biopsy specimen.<sup>20</sup>

There are several reported studies that analyze cryoablation in small human breast carcinomas; all but one performed excision of the tumor after the freezing procedure.<sup>18,20,26,32,33,38</sup>

The only case of invasive cancer treated by cryoablation without excision in humans was reported by Staren in 1997. It was a case of a biopsy-proven multifocal infiltrating lobular carcinoma in a patient who refused standard surgical therapies. The patient had negative core needle biopsies at four and 12 weeks after the cryoablative procedure.<sup>5</sup>

## Conclusion

An equal effectiveness to current surgical procedure, less invasiveness, and cosmetic superiority should

at least be proven prior to introducing a new technique for breast cancer treatment. Furthermore, guidelines must be established to ensure the proper application of this technique as a new standard treatment. However, leaving the treated tumor *in situ* after cryoablation deprives two crucial elements that are important in the clinical management of breast cancer. These are the size of the tumor and its margin status.

More effective imaging assessments that can precisely determine the three dimensions of the lesions and can differentiate tumor from benign surrounding tissue may improve the effectiveness of the treatment and add safety in subsequent follow-up.

Currently, the eventual roles of, and outcome after, ablative treatment in breast cancer are uncertain and, as are all the cryoablation studies in humans but one, were followed by excision. However, the idea of being able to perform a breast cancer treatment procedure in an office setting without the need for sedation is appealing.

Further research is necessary to establish the guidelines for patient selection, integration with other modality of breast cancer treatment, and appropriate follow-up. ■

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