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Ultrasound-guided cryoablation of breast fibroadenoma: a pilot trial

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Abstract
Purpose The aim of the study was to evaluate cryoablation (CA) under ultrasound guidance in the office setting with liquid nitrogen system for patients with fibroadenoma (FA).
Methods For this prospective multicenter trial, an office-based cryosurgical system was used to treat histological confirmed benign FA with a maximum dimension of 3 cm. Sixty CA procedures were performed under ultrasound guidance. A freeze–thaw–freeze treatment cycle was performed according to the size of the FA. During the CA procedure continuous ultrasound monitoring was performed, verifying engulfment of the FA. Patients attended four follow-up visits at 1 week, 3, 6 months and 1 year and underwent ultrasound, physical examination and photography.
Results Data were collected and analyzed in 60 cases. 59 of 60 FA (98 %) were fully engulfed by the ice ball. No serious adverse events occurred related to the IceSense3^{TM} system. At the 1-year follow-up, the FAs were gone in 93 % of the cases. Prior to CA procedure, 76 % of the FAs were palpable. Afterwards in some cases (22 %), a scar/cryo lesion was palpable. 28 % of the patients reported pain, described as mild or moderate, compared to 2 % after 1 year. Cosmetic results at 12 months follow-up were reported as good or excellent in 100 % by physician and in 97 % by patients.
Conclusions The cryodestruction of the FA using liquid nitrogen system proved functional and safe, while showing meaningful reduction in volume, palpability, pain and cosmetic satisfying outcomes.

Keywords Cryoablation · Ultrasound · Fibroadenoma · Office-based procedure · Cryotherapy · Breast

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Introduction

About 80 % of breast biopsies result in a benign diagnosis, with the most common form of benign tumors being a fibroadenoma (FA). Approximately 10 % of all women will experience a FA in their lifetime [1, 2]. In the past, there have been three treatment options for symptomatic FAs: surgical excision, vacuum-assisted biopsy or follow-up [1–6]. Now cryoablation (CA) offers another option for patients with FA [7].

The principal objective of cryosurgery is the localized destruction of the target tissue [7–10]. Clinically, cryosurgery is accomplished by placing a cryoprobe into the

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tumor under ultrasound guidance. Activation of the cryosurgery system causes cooling of the cryoprobe to extremely cold temperatures reaching a maximum of −170 °C. This results in the conductive removal of heat from the tissue and consequently cell destruction by freezing.

Multiple studies have shown that tissues, including breast tissue, exposed to extreme cold during two subsequent freeze–thaw cycles will be uniformly ablated [8, 11, 12]. CA has been successfully used to treat a variety of malignant and benign conditions, from dermatologic maladies to cancers of the liver, adrenal gland, kidney and prostate [13]. As a result of better understanding of tumor cryodestruction at a molecular level, refinements in cryo-techniques, remarkable progress in imaging and improved patient selection, the results of cryotherapy are becoming more promising. The treatment of breast diseases with cryosurgery started in 1987, and has increased rapidly since 2000 [7, 14, 15].

CA for breast FAs has previously been reported as safe and effective both acutely and at long-term follow-up (up to 3 years). At the long-term follow-up, CA as a primary therapy for breast FAs demonstrates progressive resolution of the treated area, durable safety, and excellent patient and physician satisfaction. Studies are now under way in the assessment of treating FA with CA in community-based practice settings [1, 2, 9, 16–19].

The aim of this study is to evaluate the safety and efficacy of a new office-based liquid nitrogen-based cryosurgical system (IceSense3^{TM} of IceCure Medical, Caesarea, Israel) in the treatment of breast FAs.

Secondary objectives are to evaluate cosmetic outcome, pain, physician's and patient's satisfaction of the CA procedure.

Materials and methods

Study design and patients

The CRYSTAL study was conducted as a multi-centered, open labeled and non-randomized clinical trial in 2011/2012. A total of 60 FAs in female patients were included in Prague, Czech Republic, Heidelberg, Germany, Tuebingen, Germany and Haifa, Israel. The vote of each local independent ethics committee was obtained.

The IceSense3^{TM} cryosurgical system

The principal objective of cryosurgery is the localized destruction of the target tissue by applying extremely cold temperatures. The IceSense3^{TM} Cryosurgical system uses liquid nitrogen as cryogen, which reaches cooling temperatures as low as −196 °C. It is a minimal-invasive, percutaneous procedure suitable for office setting, with only local anesthesia. Ultrasound guidance is used to guide the thin cryoprobe (up to 3.5 mm) through a stab incision into the center of the lesion. Liquid nitrogen is utilized under low operating pressure as cryogen which is controlled by the computer-modulated cryogen regulator. The cryoprobe achieves rapid freezing by means of an active freeze zone at its distal tip (in bench testing temperature measured was down to −170 °C); an isolated zone proximal to the freeze zone prevents unwanted freezing along the cryoprobe shaft. The rapid cooling allows short treatment times compared to other cryogen systems.

Within a few millimeters of the cryoprobe, high freezing rates induce intracellular ice formation which cause irreversible membrane damage and cell death. The killing of the tumor cells results from the direct (intracellular ice formation and osmotic dehydration) and indirect damage (ischemia). Farther from the cryoprobe, the majority of the iceball experiences lower freezing rates that lead first to extracellular ice formation. Ice causes an increase of the extracellular solute concentration, resulting in movement of water out of the cell, and cell death. The endothelial cells of the microvasculature are also damaged through the direct injury mechanisms, which results in vascular stasis. In the hours and days following CA, ischemic damage occurs throughout the previously frozen volume which results in uniform necrosis. The palpable or imaged tissue disappears over time [1, 2, 9, 17, 18]. The killing of the tumor cells as an immunologic response is still subject to further investigation [20].

Trial protocol

Patients of the age of 18 or older with a histologically proven FA with a maximum width of 3 cm and minimum distance of 0.5 cm to the skin were enrolled in the study. Baseline demographic data and medical history were recorded and the clinical routine including a photograph of the breasts (physical examination, imaging of the breasts). The target FA lesion was visualized with ultrasound, and a convenient and when possible esthetic location was chosen for the cryoprobe entrance site. In preparation for the CA procedure, the patient's breast was prepared with antiseptic and sterilely draped on an examination table according to the routine practice of the institute. Lidocaine, or an equivalent local anesthetic agent, was injected in the skin and along the projected CA probe path toward the center of the tumor. A small scalpel (No. 11) was used to make a puncture skin incision. The cryoprobe of the IceSense3^{TM} CA system (IceCure Medical, Israel) was inserted through the incision. The coldest zone of the cryoprobe was centered to the FA to achieve the maximum freezing effect monitored by ultrasound. This was performed using the regular technique of ultrasound-guided biopsy. Transverse

ultrasound examination confirmed the central position of the cryoprobe within the FA. In the next step, the cryogenic system was activated. All tumors were subjected to two identical freeze cycles with an interposing passive thaw. Continuous ultrasound monitoring documented the size of the ice ball forming around the cryoprobe. The treatment duration was determined based on FA size. The end point of the first freeze cycle was reached, when the ice ball engulfed the tumor completely. In most cases, the thaw time was identical to the freeze time unless additional time was needed due to specific clinical procedures (e.g., saline injection). In case of close tumor proximity to the skin sterile saline was injected between the skin and the forming ice ball, increasing the distance and protecting the skin from thermal injury. The end point of the second freeze was to engulf the tumor.

Due to the cold temperature at the end of the procedure, the probe was adherent to the tissue. Therefore, the physician was required to wait a short moment while actively heating the tip of the probe for easier and safe detachment from the patient's breast. The ice ball size, skin appearance, and patient comfort were closely monitored during the procedure.

If no complications occurred, patients were promptly released after the procedure. Post-procedural expected pain is minimal; patients were advised to take mild analgesics, if necessary.

Patients attended follow-up visits at 1 week, 3, 6, and 12 months and underwent clinical breast examination, ultrasound and photograph. At each visit, the patients were asked to report on adverse events, lump palpability and consistency, severity of pain, cosmetic results as well as satisfaction with the results of the procedure.

Data were analyzed based on engulfment of the FA by the ice ball in every cryotherapy procedure monitored by ultrasound imaging. The tumor volume reduction following CA procedure was assessed by ultrasound. This was based on the assumption that the FA is approximately ellipsoid with negligible differences. Therefore, the volume was calculated according to the formula for a prolate ellipse:

$$V = \frac{\pi}{6} \times \text{length} \times \text{width} \times \text{diameter}. \quad (1)$$

The data were analyzed using Access data base (Microsoft, Unterschleissheim, Germany) and Excel (Microsoft, Unterschleissheim, Germany).

Results

In 2011 and 2012, data were collected from 60 procedures which were performed at the four sites. A comparison of pre-cryotherapy procedure status of each patient and FA and the status 1 year after the cryotherapy procedure was performed in patients who finished the trial ($N = 58$ out of 60), which included addressing lump palpability and consistency, pain and satisfaction. 2 patients out of 60 had partial follow-up due to change in residence.

Functionality

Engulfment was achieved in 98.3 % (59 out of 60) of the cases, as verified by ultrasound imaging. In a single case, the FA tumor was nearly engulfed due to off-center positioning of the probe. This resulted in 2 mm of the tumor not being engulfed by the ice ball at the end of the freezing cycles. At 1-year follow-up, only scar tissue was seen in the ablated area under imaging.

The first freezing cycle took an average of 1:44 min, while the duration of the second cycle had an average of 1:30 min.

In one case, the FA was undertaken only one freezing cycle due to a superficial location of the FA, which achieved full engulfment. Despite that at 1-year follow-up, there was only scar tissue in the ablated area, as seen under ultrasound imaging.

Safety

No serious adverse event occurred either during or out of the study that is related to the IceSense3^{TM} system. One mild and resolved adverse event occurred during the study that was reported as induration in the patient breast. The induration was surgically removed and from pathology analysis it was not related to the IceSense3^{TM} system device, protocol or to the CA procedure.

Lump palpability

The palpability of the lump was assessed pre-treatment and at the 1-year follow-up visit

Prior to CA procedure, 76 % (46 out of 60 patients) of the FAs were described by the patients as palpable compared to 22 % (13 out of 58, data are missing for 2 patients) after 1 year post CA procedure. As described in the literature, scar tissue can be described as palpable lump [21].

The graph shows the process of reduction in palpability which is a normal biological process which happens over time (Fig. 1). In most cases, scar tissue of various dimensions similar to surgery scars were palpable and confirmed with ultrasound imaging which disappeared over time.

Pain

The patients were asked to rate the severity of pain caused by the lump prior to cryotherapy and 1 year post CA as none, mild or moderate.

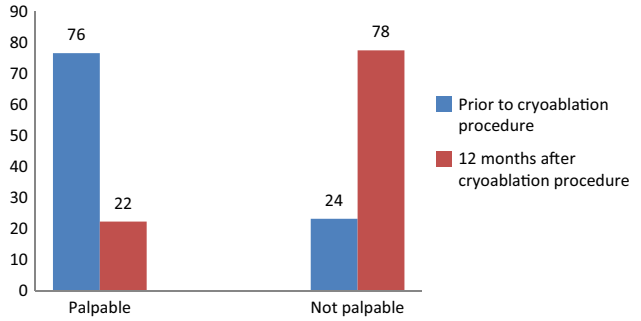

Fig. 1 Development of the fibroadenoma palpability, prior and 12 months after cryoablation

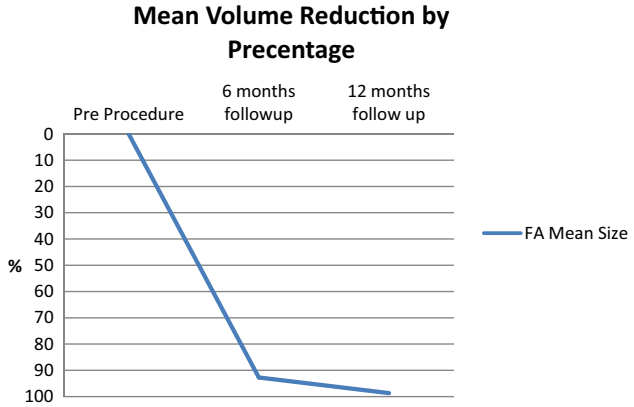

Fig. 2 The mean volume reduction at 6- and 12-month follow-up

Prior to CA procedure, 28 % of the patients reported pain, described as mild or moderate, compared to 2 % after 1 year.

No pain was reported during the procedure of cryoablation.

Physicians' and patients' satisfaction

Physician and patient satisfaction was evaluated on a scale of 1 (poor) to 4 (excellent). Regarding cosmetic results, the results at 12-month follow-up were reported by physicians as good or excellent in 100 % of the cases and by patients in 97 %. Two patients described the results as medium.

The photographs taken prior to the procedure and at 1-year follow-up of CA were compared and showed no cosmetic difference. The size of the breast, the shape and volume were unchanged.

Volume reduction

The lump volume was assessed by ultrasound measurements pre-treatment and at the 1-year follow-up visit. The mean volume of all FAs was 1.2 ± 0.9 cm^3 (range 0.12–5.1 cm^3) prior the cryotherapy.

In addition, in the follow-up visits, residual debris called cryolesions, was examined on US by the physician but not considered as FA tissue. Therefore, the volume measured was calculated as a cryolesion. By considering these reports, it is reasonable to deduce that the FAs were completely gone in 93 % of the cases after 12 months leaving only scar tissue (Fig. 2). Finally, the US images below show the progressive response to CA with a resolution process that continues over a year (Fig. 3a–d).

Discussion

The functionality and safety of the system was proven, as 98 % of the FAs were engulfed by the ice ball obtained during the procedure and no serious adverse event related to the IceSense3^{TM} system occurred. The CA procedure may create necrotic residues (scar, etc.) at the treated area that can be seen under ultrasound exam and may be palpable. Throughout the follow-up visits, the ultrasound appearance changes from the mass getting concentrically smaller to taking on a highly irregular appearance (not circumscribed margin, mixed echogenicity, etc.) [22]. The measured volume can be reported as a cryolesion. Therefore, it is reasonable to deduce that a gradual resolution can be observed.

The median volume of the FAs was significantly reduced comparing the pre-CA to the 1 year post CA (in 93 % a reduction of 100 % was achieved). The other assessed parameters as the palpability, pain and physicians' and patients' satisfaction are subjective and rely on personal perception. Lump palpability showed a significant improvement in comparison to palpability results prior to CA procedure. Prior to CA procedure, 76 % of the FAs were palpable. Afterwards in 22 % of the cases were palpable. In correlation to the ultrasound imaging, these findings most likely were scar tissue. Comparing this with surgical excision these results are promising. The number of palpable lesions was reduced by more than 50 % and no scars or sutures with the exception of minimal scars of the puncture site remained.

At 1-year follow-up, cosmetic results were reported as excellent or good in 100 % of the cases by physicians. Patient satisfaction was reported as good or excellent in 97 % of the cases. Two patients describe the result as medium.

It is difficult to compare the efficacy of this method with other studies from the literature. Due to the lack of a postoperative histological exam and all measurements being based on imaging, the amount of volume reduction cannot be compared precisely. Influencing factors may be the size of the ice ball, the freezing rate, the very low

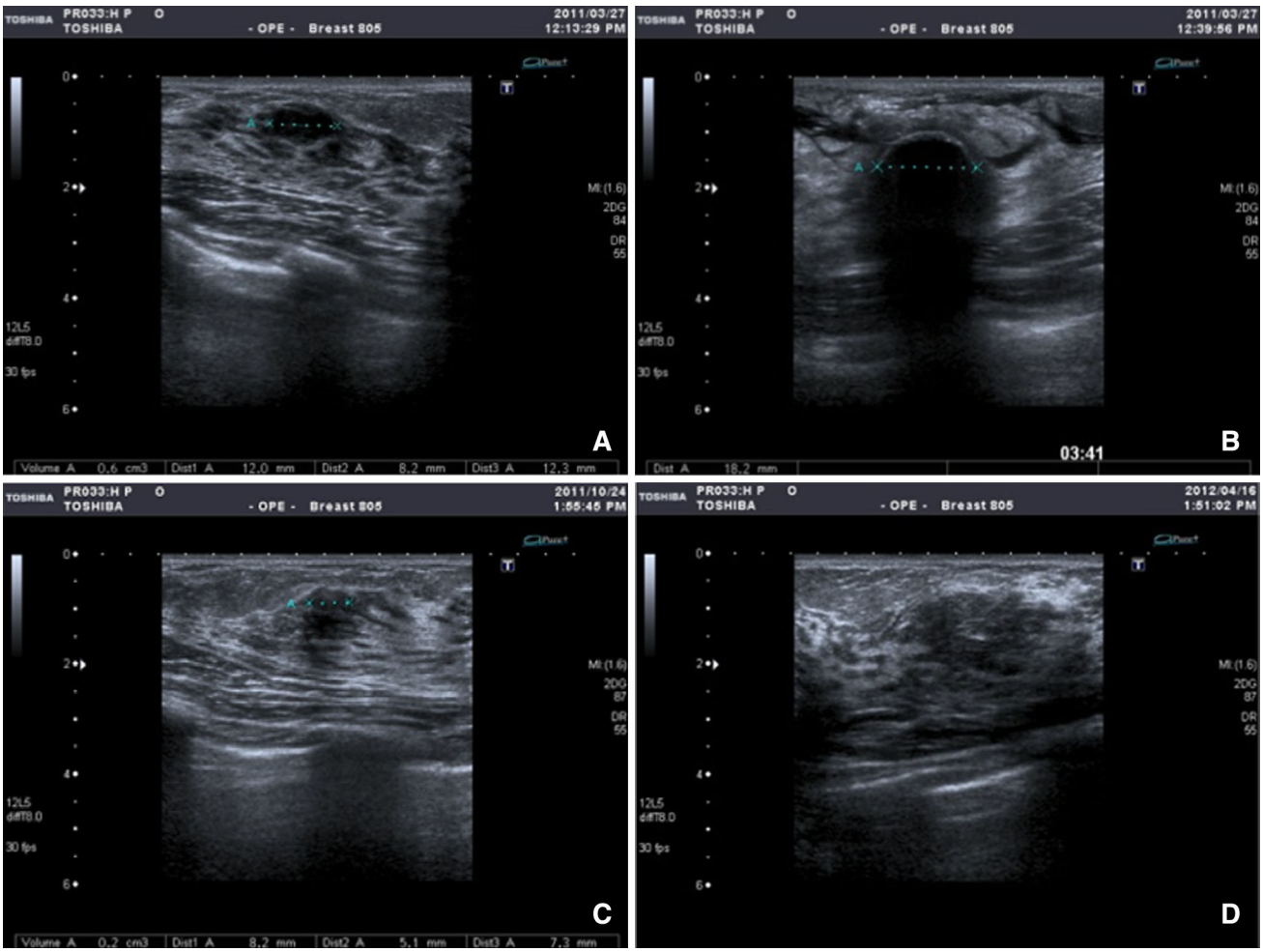

Fig. 3 **a** FA before cryoablation. **b** FA during cryoablation with an iceball engulfing the FA completely. **c** Cryoablated area after 6 months. **d** Cryoablated area after 12 months

freezing temperatures and the number of freezing cycles. Our results are comparable concerning the effect of volume reduction, palpability reduction and complication rate to those of Kaufman et al. [1, 2, 21] who also reports of a 12-month follow-up. On a voluntary base, we followed up some patients also after 24 and 36 months. The prior cryolesions showed no further change.

We are aware of two possible main errors that can influence the measurement results: the ultrasound measurements and the limited number of patients [23].

We will neglect the ultrasound measurement error since all measurements of one patient were taken by the same physician on the same ultrasound system and using the same method. Therefore, it is a systematic error assuming that the same error occurs and has the same influence on all of our results.

This study is limited by the number of enrolled patients. Thus, we were able to confirm the results of an earlier study and the results of Kaufman et al. [1, 2, 21] show similar good functionality and effects of CA. The next step could be to evaluate the treatment of small breast cancers with CA [24, 25].

Since about 10 % of all women will experience a FA during their lifetime and many wish to be operated on the FA, there is a great demand for minimal-invasive procedures as, e.g., CA [1, 2]. Minimal-invasive procedures as CA offer several advantages in comparison to the standard surgical procedure for the patient and are therefore preferred. The advantages especially refer to the better cosmetic outcome without a remaining scar and that no breast tissue needs to be removed. Therefore, the size and shape of the breast remain unaffected. In addition, the procedure is considerably shorter and can be performed office-based with only local anesthesia instead of general anesthesia. This is especially beneficial for women with multiple FAs.

Conclusion

In conclusion, the liquid nitrogen CA procedure proved to be safe and effective, while showing a complete FA volume reduction of 93 % of the lesions and pain reduction from 28 to 2 %. Also the high rates of the patients' and physicians' satisfaction at 1 year post CA follow-up demonstrate the efficacy of this technique and makes CA a desirable option compared with other treatment options for FA.

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Conflict of interest The authors declare that they have no conflict of interest.

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