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CHAPTER 9

Cryosurgery or Cryoablation: The Future of Breast Cancer Treatment

A Short History

Cryoablation, also called cryosurgery, cryotherapy or targeted cryoablation therapy, refers to the application of extreme cold to destroy diseased tissue, including cancer cells.

PubMed offers this background.

"The use of freezing temperatures for the therapeutic destruction of tissue began in England in 1845-51 when Dr James Arnott described the use of iced salt solutions (about minus 20 degrees C) to freeze advanced cancers in accessible sites, producing reduction in tumor size and amelioration of pain. Improved freezing techniques were possible early in the 1990s when solidified carbon dioxide came into use and later when liquid nitrogen and nitrous oxide became available. Nevertheless, cryotherapy was a minor technique, used only for the accessible lesions of skin and mucosa. With the development of modern cryosurgical apparatus by Cooper in 1961, a resurgence of interest in cryosurgery was initiated and techniques for diverse clinical conditions, including visceral or abdominal cancer, evolved. After the initial widespread clinical trials matured in the 1970s, some applications of the technique fell into disuse while others became standard treatment. Late in the 1980s, further improvements in apparatus and imaging techniques have permitted increased clinical use in neoplastic disease, including visceral cancer".

Cryotherapy has been used for cervical abnormalities in females as standard of care for at least 40 years. Cryotherapy is used to destroy skin tumors, precancerous skin moles, nodules, skin tags, or unsightly freckles. With the improvement of imaging techniques and the development of devices to better control extreme temperatures, physicians are using cryotherapy as a treatment for patients with breast cancer as well as other forms of cancer including liver (usually metastasized from other organs), lung, kidney tumors, prostate cancers and pancreatic cancer. Breast cancers are much easier to freeze since the tumor is sitting in fatty tissues with very few large blood vessels or large nerve tracts to get in the way.

The cryotherapy technique can also be used now to help women with fibroadenoma breast issues instead of cutting the fibroadenoma out of the breast. Fibroadenomas frequently cause pain and can become quite large. They are usually more of a problem in the younger women, but most women worry about any lump they are walking around with. Cryoablation would be a simple approach to these concerns of fibroadenomas. In an article by Dr Peter Littrup et al entitled "Cryotheraphy for Breast Fibroadenomas" in the journal *Radiology*, August 2004, the conclusion was "Cryotherapy of fibroadenomas is safe, effective and virtually painless done as an outpatient procedure as a treatment option with good cosmetics".

Over the past ten years, I have been dealing with 42 radiology centers in Oregon, Washington, California, and Idaho. My favorite radiologist, Dr. Cindy Tortorelli, who is now at EPIC Imaging in Portland, Oregon, previously had been freezing fibroadenomas for over a decade at the Mayo Clinic where she worked in the women's breast imaging department. I hope that in the near future, Dr. Tortorelli will be able to bring cryoablation equipment to Portland, Oregon so I will have a trained radiologist available to whom I can send patients for fibroadenomas and breast cancers.

How I Became Interested in Cryoablation and The Cryo Pioneers

Another technique that I hope will become the worldwide standard of care for breast cancer is called cryosurgery, cryotherapy or cryoablation. I was fortunate enough to work with two women who had this procedure done by Dr. Peter Littrup, an interventional radiologist who at the time was at the Karmanos Cancer Center in Detroit. Dr Peter Littrup is now at Crittenton Hospital in Rochester Michigan as of spring 2017 and I am in contact with him as well.

Laura Ross-Paul is the "Patient Pioneer" of cryoablation and she received her cryotherapy treatment in 2003 at the Karmanos Cancer Center in midtown Detroit, Michigan, one of 41 National Cancer Institute's designated Comprehensive Cancer Centers in the U.S. and the only hospital in Michigan dedicated exclusively to fighting cancer. Laura is the first woman internationally to have her breast cancer frozen.

Dr. Peter Littrup had received FDA approval for a device that he first invented and used to freeze prostate cancer tumors in place using liquid nitrogen years previously. Alex Paul, Laura's husband, contacted Dr Littrup and asked if they could come see Dr Littrup and asked if cryotherapy could be used for the two biopsy proven breast cancers that Laura had. Dr Littrup said it had never been done before but it was a good application for cryoablation, and he told them to fly to Detroit. Thank goodness for out of the box thinking!

Laura Ross-Paul has co-written a book with her husband, Alex Paul, and her cancer physician, Dr. Littrup, titled *They're Mine and I'm Keeping Them*, which documents the story of how she and her husband bucked the system and found Dr. Littrup, whose advanced skill in the field of cryoablation ultimately saved her breast.

What is Cryoablation or Cryosurgery All

About?

Now let me get back to discussing what cryoablation or cryotherapy is all about. Here is a short overview. This is taken from *They're Mine and I'm Keeping Them*. Check out Laura Ross-Paul's book for yourself from my bookstore at www.ProtectYourBreasts.com books/theyre-mine-im-keeping-freezing-breast-saved-breast/.

She writes:

"The body's immune system is able to recognize the protein structure of the cancer cells when it cleans out the dead tissue and in about half the cases of cryo-ablation, naturally creates an immunity to the cancer. The book also relates the success at FUDA Hospital in Guangzhou, China in treating a variety of Stage 4 cancers by combining cryo-ablation and advanced immune system therapies, which increase the frequency of the occurrence of the natural immune effect to approximately eighty percent or higher of the breast cancer cases".

"Cryoablation is used in a variety of clinical applications using hollow needles or cryoprobes through which cooled, thermally conductive, liquid nitrogen is circulated. Local anesthesia is administered to the surface of the breast and then cryoprobes are inserted into or placed adjacent to tissue that is determined to be diseased in such a way that ablation will provide correction yielding benefit to the patient".

"When the probes are in place, the cryogenic freezing unit removes heat ("cools") from the tip of the probe and by extension from the surrounding tissues."
"Ablation occurs in tissue that has been frozen by at least three mechanisms:

(1) The formation of ice crystals within cells thereby disrupting membranes, and interrupting cellular metabolism among

other processes

(2) Coagulation of blood thereby interrupting blood flow to the tissue in turn causing ischemia and cell death

(3) Induction of the so-called programmed cell death cascade
"Cancer survives in the body by camouflaging itself from the immune system. After a tumor is frozen, the body absorbs the dead tissue. The protein structure of the tumor remains intact after freezing, so the immune system can "see" the cancer and recognize that it is a foreign body. When it does, this triggers a complex immune process that often builds antibodies to the cancer. These antibodies then kill other tumors throughout the body. This is the Immune Effect."

I have demonstrated this to my own patients by holding the fist of one hand up against the palm of my other hand. I then tell the woman that the fist represents the cancer which is a parasite and living off the organ that it has invaded, represented in this case, by my palm. My body cannot "See" the cancer and it continues to provide oxygen and nutrition to this parasitic cancer. However, once the cancer has been frozen with liquid nitrogen, the body and your immune system can recognize this foreign invader and destroys it.

~~Laura Ross-Paul calls herself a "Patient pioneer," as one of the first women in the world to receive cryoablation by Dr. Littrup as the primary treatment for her multi-focused breast cancer. Laura and her husband Alex Paul had been searching for an option other than a mastectomy back in 2003.~~

Dr. Littrup has since been doing clinical studies using this technology to freeze breast cancer tumors by injecting them with liquid nitrogen to freeze the tumor in place. This therapy completely conserves the breast. Surgery is not necessary and the cryoablation kills the cancer as well as in any satellite breast cancers in other regions and lymph nodes 85% of the time as part of the immune effect. Cryoablation of cancer leaves tumor-associated antigens that stimulate an anti-tumor immune response.
If anything should return

in the 15% of the women for whom the immune effect did not work, they could have another cryotherapy or have surgery as the third back up plan, not the first as it is currently.

I have become friends with Laura Ross-Paul and she and I are trying to network and raise awareness of this life and breast-saving technology. We are also trying to bring cryoablation to the Pacific Northwest at the time of publication of this book. ~~I will share more of Laura's story a bit later in this chapter and provide links to her book and website so you may explore this ground-breaking technology in greater depth.~~ I have expanded my new website www.ProtectYour-Breasts.com to have a whole section on cryoablation as well as interesting articles and abstracts.

I have also been sending women to other clinics that are providing cryoablation so they can get the care that they desire until we have the technology here in Oregon and Washington. There are clinical trials going on in different clinics across the US right now.

Information From the Fuda Hospital Brochure entitled "How to Treat a Cancer Patient"

~~Alex Paul provided this direct quote from their book regarding information~~

Fuda Hospital in Guangzhou, China in treating a variety of stage four cancers by combining cryoablation and advanced immune system therapies. Fuda Hospital provided this direct quote from their brochure that they give to their English speaking patients. These quotes are authorized by a team of doctors and scientists at Jinan University School of Medicine and the Fuda Cancer Hospital. Check out their website at

http://www.fudahospital.com/en_asp_new/

I think this is helpful to see why cancer is considered by many, to be a chronic disease.

"Cancer is a systemic disease with tumors as a local manifestation of the disease. Once cancer occurs in a person, cancerous cells may metastasize (spread) throughout the whole body. Surgical removal of the tumors in no way implies that one is cured of cancer. For example, breast cancer can relapse even if the original tumors were removed".

"Like hypertension and diabetes, cancer is a chronic disease. The disease may take a few years to manifest itself, from its occurrence until the emergence of tumors. In some cases, cancer cells may exist in a stage of dormancy and never manifest themselves".

"Our immune system plays an important role in controlling the development of cancer. Cancer cells may either be killed by immune cells or if they are as strong as the immune cells, nothing happens in the body. However, if the amount of immune cells decreases, leading to a decrease in their activity levels, or if cancerous cells are able to evade the detection of immune cells (a process known as immune tolerance), then the cancerous cells will spread rapidly and become life threatening".

"Influenced by various factors inside and outside the body, a series of genes mutate continuously so tumors are formed. Though cancer patients may be suffering from the same cancer, their pathogenic factors and mutational genes differ. Every tumor has its specific biological features, or heterogeneity. Ignoring the heterogeneity is the main reason that cancer treatments often cannot achieve their ideal effects. It will work better if more personalized treatment is prescribed to deal with the heterogeneity".

"The complete cryoablation of the tumor is done to minus 160 degrees Centigrade or lower. Later the temperature is raised to 20 to 45 degrees C with warm packs. This is repeated two or three times resulting in the complete ablation of the tumor. After cancer cells have been destroyed by the cryoablation they are left intact. Dead cancer cells

will release antigens stimulating the immune system to eradicate any remaining cancer cells and reduce recurrence of cancer".

This "Immune effect" I feel is far superior to just surgery alone or surgery with radiation or chemotherapy which damages the immune system. Your own body is quite clever in trying to heal itself.

Some Other Interesting Articles on Cryoablation

In order to try to keep up with new research as it is made available in the future, I will be posting articles and links on my website so you may review the current literature at www.ProtectYourBreasts. I am expanding the cryotherapy section.

This was an interesting article in *Annals of Surgical Oncology*; July 2016 entitled "Exploring the Success of Cryoablation Therapy in the Treatment of Invasive Breast Cancer". There were 86 women in the study and 92% of them had a successful ablation of their tumors.

There had also been a small Japanese study that showed that of the women who had undergone cryotherapy, 47% of them were still in remission after five years. These were women who previously had end stage 4 inoperable breast cancer and no other therapies had been used besides doing cryoablation! If these women had been here in the United States, they probably would have been told to "Put your affairs in order since they would have been considered terminally ill".

Here is another article that tells what is happening inside the cells when cryotherapy is used.

In a Japanese study from The Kameda Medical Center, The Eisuke Fukuma Chapter in 2016 looked at "Non Surgical

Ablation Therapy for Early-stage Breast Cancer" and they provide the mechanism for what the freezing is doing to cells. "The mechanism to destroy tumor cells with cryotherapy occurs by four mechanisms:

(a) Rapid cooling (intracellular freezing): ice crystals are formed inside and outside tumor cells destroying the cell membrane directly causing mechanical stress.

(b) Slow cooling (extracellular freezing).

(c) Flow of intracellular fluid to extracellular space causes shrinkage of the cells.

(d) During time of thaw, influx of water from extracellular space to inside of the cell results in overexpansion of the cell, followed by mechanical stress and destruction of cell membrane. Outflow and influx of water in the cell causes rapid change of osmotic pressure and concentration of electrolytes (osmotic and chemical stress).

My Personal Thermography Observations of a Woman Pre- and Post-Cryoablation

I invite you to view the first known infrared images of a patient, Mary L., who came for a thermography scan prior to having cryoablation done on her left breast by Dr. Peter Littrup on 4-27-2010. Please visit my home page at www.ProtectYourBreasts.com in the cryoablation section. There are YouTube and Webinar links for you so you can follow along with the images.

Mary L. Infiltrating Ductal Carcinoma Three Months Pre-Cryoablation

I personally came to be introduced to the cryoablation technology in 2010, prior to meeting Laura Ross-Paul. A woman named Mary L., who lived in the Portland, Oregon area, wanted to come to see me to do a thermography study. Mary came to me early in 2010 after being diagnosed in December,

2009 by needle biopsy with an infiltrating ductal carcinoma Stage II tumor in her left breast at 12:00 that was two cm by two cm in dimension by breast MRI with and without contrast (1-29-10). Mary had a very abnormal thermogram with a two degree Celsius Delta thermal shift over the mass and blood flow leading to the tumor that I was able to palpate. The size of the tumor was also substantiated by a previous ultrasound done prior to her needle biopsy. A left axillary lymph node had a lobulated and thickened cortex.

Pre-cryoablation, she had dimpling above the left nipple at 12:00 and a mass as noted above with increased caliber vessels leading to the area of her tumor. The red circle surrounds the region of the tumor, which was warmer (as indicated by the Celsius scale to the right if you are looking at the slides on my website home page under cryoablation. Please view these slides now so you can follow along).

Mary had refused standard surgery, radiation, and chemotherapy, and she had been able to be seen in Detroit at the Karmanos Cancer Center by Dr Littrup, after she had contacted Laura to find out about this technology. Mary's cryoablation procedure took about 35 minutes in an office with an ultrasound machine. The cryoablation was done with local anesthesia. A hollow probe was inserted into the tumor, guided by ultrasound and liquid nitrogen flowed through the probe to create an ice ball extending two cm out beyond the tumor margin in a 360 degree freeze zone. Warm compresses were applied shortly afterwards to melt the ice ball. Dr. Littrup froze the tumor and any suspicious lymph nodes that were seen by ultrasound.

After the procedure, Mary went out for lunch with her daughter and later in the day took two Tylenol. Pretty amazing!

Dr. Littrup told me that some women do not even take the day off and go back to their offices after the procedure. Since cryoablation is using extreme cold, this freezing also acts as a cold cautery and any small blood vessels are shut off due to the freezing so there is little bleeding. In addition, the

freezing has an additional numbing effect so many women have said that the cryoablation was much less uncomfortable than a needle or core biopsy.

Mary L. Infiltrating Ductal Carcinoma Eight Months Post-Cryoablatiion

I am inserting a special warning to patients and their physicians here. Never surgically disturb or biopsy the spongy mass post-cryoablation. **Necrotic tissue can show up in mammography until fully resolved so it is important for patient to tell imaging specialists that she has had cryotherapy and that they should not try to biopsy it.**

I saw Mary again for a thermogram eight months after the cryoablation and the mass was now large and spongy and the region was 4 cm by 6.5 cm across. The hard mass previously had been two cm by two cm. On my exam eight months after cryoablation, there was no thermal activity over the soft spongy mass and the blood vessels that were observed three months prior to her cryotherapy procedure that were leading to the tumor were now absent.

Remember from an earlier section of this book that I mentioned that when infiltrating ductal carcinomas as well as lobular cancers achieve a certain size, the cancer cells start emitting nitric oxide, which is a vasodilator that keeps the blood vessels open so tumors have greater access to oxygen and nutrition, which then encourages tumor doubling times. You can see these vascular changes by following the link to the slides on my website in the "Save Your Breasts" section.

At first, I was alarmed by the size of the soft spongy mass since it had doubled in one direction and tripled in the other direction. Dr. Littrup told me that this was common after cryotherapy due to the immune effect, which occurs in about 85% of the time in the woman's own body. The body's immune system is able to now recognize the protein structure of the cancer cells and the body sends out white blood cells and cytokines to clean out the dead tissue that the liquid nitrogen had frozen and this naturally creates immunity to the cancer.

If you now continue to view Mary's slides you can see the pointer views on the infrared images that demarcate the borders of the spongy mass, which was 4 cm by 6.5cm. The thickened area is blue and scanned cold or was hypothermic on IR.

If you undergo a cryoablation procedure yourself or someone you know does, it is of utmost importance to never surgically disturb or needle biopsy the spongy area, which is comprised of dead tissue and white cells that are attacking the area. If you do, this will greatly interfere with your body's immune system response to break down the dead cancer cells and you may well cause an infection in the area that could become life-threatening. Allow your body to do the healing and do not let a surgeon or radiologist interfere with the process by cutting into the area or doing any sort of biopsy. Laura Ross-Paul and Dr. Littrup have both mentioned this to me.

Mary L. Two Years Post-Cryoablation

I saw Mary again two years after the cryotherapy and the residual tumor was now only 1.5 cm and had become a thermally inactive, cold, inert mass of scar tissue without any blood flow or neoangiogenisis leading to the area shown in the red circle on the post cryoablation slides. Dr. Littrup told me that several months after the cryoablation is done and the tissue becomes spongy as the immune effect starts to heal the tissues, the spongy mass shrinks about 80% in size leaving a small bit of scar tissue. Scar tissue on infrared scans cold since there is no thermal activity. Mary was also instructed to follow the Proactive Breast Wellness protocol. These cryoablation results were amazing to me! Please share the slides and information on my website with as many people as possible!

Why Aren't We Hearing About Cryoablation?

You must be saying to yourself, "Why on earth have I not heard about cryotherapy or cryoablation from my doctor or oncologist?" Why haven't you seen information on the news? If cryoablation works so well at killing off breast cancer cells, not only in the tumor but also 85% of the time in lymph nodes and satellite lesions, why does no one know about this?

Cryotherapy to treat malignant breast tumors is still considered experimental even after 14 years and thousands of women treated in China and other countries internationally and even though there is very little risk of harming anyone using this technology. The ice ball created around the tumor simply melts.

I personally feel the reason cryoablation is not being embraced is that it works too well and it would be taking money away from the "cancer machine" by which physicians make more money when people are ill. There is little incentive to do a 20 to 30 minute office visit with ultrasound to freeze a cancer that might never come back again. US medicine is an illness-based system, not a prevention-based system. Women are the pawns on the allopathic medical chess board.

I recently conducted a local survey here in Eugene, Oregon when a fee-for-service patient of mine without any insurance wanted to know what a simple mastectomy might cost her and her family. She had a very abnormal thermogram and I had begun to send her through the system to get structural studies done, a biopsy, and a surgical consult. When she asked me how much it would cost, I did not know, so I started calling offices at the hospital to find out. It was eye-opening for me.

I called the following offices: radiology to get the costs for mammogram and ultrasound; pathology to find out about the cost of needle and excisional biopsy samples. Then I called one of the local surgical groups to find out about the

costs for the surgical consult prior to surgery, the surgical procedure itself, and post-op visits. Then I called the anesthesia department to get the pre-surgery anesthesiology visit charge and cost for the anesthesiologist's services during surgery. Then I called outpatient day surgery and asked also what it would cost for hospital facility fees if there was an overnight stay, plus post-op care in the recovery area, IVs, medications, etc. After all these calls, I discovered a simple mastectomy in Eugene, Oregon ranged between $57,000 and $57,500! These fees may be higher in other regions of the U.S.

I was shocked and amazed to know how much this would cost this farmer's wife who was home schooling her kids, and who currently had no insurance!

As a post script in this case, I want to let the readers know that I also contacted the hospital social services department and after several phone calls, I was able to get this woman enrolled in the Oregon Health Plan/Obama Care so that her upcoming breast cancer treatment would not bankrupt her and her family.

Unfortunately, this financial forecast of what breast cancer costs a woman is not yet complete. Now these previously mentioned medical/surgical fees do not take into consideration what might come next for this woman if she were sent to medical oncology for chemotherapy or radiation oncology or, worst case scenario, to both departments if she had an invasive cancer with positive lymph nodes. This woman might also be put on estrogen blockers like Tamoxifen and be subject to the costs and medical oversight that go along with that. This was harder for me to estimate, but several of my client cancer survivors who had gone that route told me that, conservatively, that might total another $50,000 or $60,000 or more on top of the surgery. You might easily be up over $110,000 to over $120,000 to treat your breast cancer!

You can now see why I have been so passionate about promoting "Prevention IS the Cure!" after learning the financial strain as well as the emotional and physical suffering

a woman and her family go through after being handed a breast cancer diagnosis.

Why Insurance Companies Have Been Slow Pay to Freeze Your Breast Cancer

Depending on whether you can get into a cryoablation clinical trial in this country, you might currently be looking at $2,800 to $4,500 for your short cryo out-patient office visit and the cryo probe cost. Several of the cryo-clinics are still trying to bill insurance for the procedure. Since cryoablation is still "investigational/ experimental" for breast cancer patients, insurance companies do not want to pay for it currently, which I think will start to change. Insurance companies might pay $2,800 for the fibroadenoma CPT code, but you cannot use the fibroadenoma code for a breast cancer even if it will likely take the same amount of time to do as an office visit. It is the same procedure to treat a fibroadenomas or a cancer with cryoablation.

This lack of attention by insurance companies has begun to anger me and I hope there are a few women who are reading this book who are willing to start taking some action to change this insurance ruling. The insurance companies' position to not recognize cryoablation for breast cancer severely harms women and prevents us from getting the care for our breast cancers that we want and need.

I think we as women need to approach some feisty militant women's groups that will take action and force this into the spotlight. I think it also could be framed as a human rights/ women's rights issue. A man can appear at the office of a urologist pretty much anywhere in the country and have his prostate cancer frozen by cryoablation and the insurance company pays for the procedure using the CPT code for freezing his prostate cancer. At the time of publication of this

book, there aren't any CPT codes for cryoablation for breast cancers. They have a CPT code for freezing fibroadenomas but not for freezing a breast cancer so the local insurances are for the most part not recognizing cryoablation. They have been paying to freeze cervixes for over 40 years, but not breast cancer.

If men can have their prostate cancers frozen, why can't women have their breast cancers treated by the same technology that works so well for the men? Breast cryoablation now has a 14 year history. Why should it still be "Investigational"?

The Chinese are setting up clinics all over their country and have done thousands of successful treatments.

Just two months prior to this book's publication, I learned that insurances in five states had begun to pay for breast cryoablation some of the time. These states are: Florida, Alabama, Texas, Michigan and Georgia. The major insurances That are paying are: Medicare/ United Health Care, Cigna, Aetna and BC/BS. There are another 15 to 20 smaller more local insurances that have begun to pay in 19 other states and the numbers are growing. This procedure will save the insurance companies thousands of dollars that they are currently paying out for "Standard of care costs for breast cancer". So my hope is that once there are more cryoablation clinics available to more women in more states, there will be more insurances paying for this treatment.

I think the other point is the huge difference in what the insurance company has to pay out for treating one case of breast cancer. I imagine they might decide that $2,800 to $4,500 looks a lot more cost effective than $110,000 to over $120,000 per woman.

Minimally Invasive Breast Cancer Cryotherapy Largely Ignored in U.S.

I have taken a couple portions ~~the following~~ from the Breast Cancer News article March 29, 2016 by Charles Moore after interviewing

Laura Ross-Paul. Her article in Breast Cancer News is also available on my website in the cryoablation section.

This Breast Cancer News article was also the most reposted article in all of 2016, so you can see that there is tremendous interest in this! Laura and I were delighted that we are beginning to get some traction in the journals, but we obviously need more exposure in the media. If you are reading this and feel that you or an organization that you know may assist in championing this, please contact us!

Cryotherapy Benefits

From Charles Moore's article in *Breast Cancer News,* Ross-Paul contends that:

"In America, cryoablation is seen as a treatment that needs to be proven effective before it is considered a safe alternative to the mastectomy and lumpectomy. FDA trials have been undertaken in the last 13 years, but the size of the trials has been limited due to financial constraints. As a result, when a doctor advises their patient who has breast cancer, cryoablation is considered as an unproven, experimental alternative to the much safer and statistically proven surgery".

"Without statistical proof through trials," she said, "cryoablation won't be used. But if cryoablation isn't used, there will be no statistics. This has doomed cryoablation in the U.S. to forever be an experimental treatment. To get around this dilemma, we believe that prevention is the key. Through early detection, women are finding something suspicious in a mammogram. Since it is not yet identified as cancer, they are told to wait and see if it develops. If it doesn't, after a long time of fearful waiting, there is a joyful sigh of relief. If it is cancer, however, at that point, cryoablation is not considered and only surgery is advised."

Laura Ross-Paul and I have been upset by this.

Meeting Laura Ross-Paul and Considering the Perfect Marriage of Thermography and Cryoablation

In April 2016, I was finally privileged to meet Laura Ross-Paul after I had begun to delve into the cryoablation literature after doing an infrared scan of Mary in 2010. I then found Laura's ~~on her~~ website and after read her book, *They're Mine and I'm Keeping Them*. In fact, she had become so excited about what I was doing using my infrared camera and the Proactive Breast Wellness program that she wanted to experience what I had to offer first-hand. She felt that what I was doing was so important in the realm of breast health and breast cancer prevention that she brought the whole Ross-Paul Clan down for a clinical day of thermography. She invited her two sisters, her daughter, and her niece from Portland, a two-hour drive for infrared exams for all of them. I also went over the Proactive Breast Wellness program with all of her relatives. If you wish to see some photos from their field trip go to visit ProtectYourBreasts.com.

After this meeting, Laura and I began to spend a lot of time networking and brain storming on the phone and through emails to see how we might be able to bring cryoablation to the Pacific Northwest and beyond. She also introduced me to Dr. Peter Littrup, so I began to have these discussions with him as well and gain his insights. Alex Paul, Laura's husband and co-author of their book, also provided some historical perspective and practical suggestions on how to move cryoablation forward.

The *"Early Freeze Protocol"* and What Women Want

As Laura, Alex, and I continued our discussions, it became clear to all of us that the medical establishment and the FDA move at a snail's pace. It had been 14 years since Laura became the first woman internationally to have had

her breast cancers treated successfully by freezing them in 2003. What we discovered was there were major hurdles regarding who would put up funding for clinical studies if the physicians felt that they would lose money when the woman did not go through the current standard of care of surgery, radiation or chemotherapy. If there weren't large scale clinical studies here in the US and if there weren't statistics, cryotherapy would be doomed to being experimental as a breast cancer treatment.

Maybe there was another way to think about this.

I first came up with some parallel thinking in regards to the way physicians currently treat a suspicious finding on a Pap smear. I shared my idea with Laura and Alex and we began to brainstorm to see how we might be able to present cryotherapy to physicians in a more palatable way. This was the start of what we now call "*The Early Freeze Protocol".*

This is what I gave as my example to Laura and Alex during our brainstorming session. If a woman is going to see her OB/GYN for her annual Pap smear and later receives a call from the physician that there are some "suspicious findings" on the Pap report, the doctor would suggest that she return to the office for a cone cryo of the woman's cervix. This is a simple office procedure that freezes the cervix with liquid nitrogen after which the woman returns in six months for another Pap smear to make sure that everything has resolved. The woman is not being treated for cervical cancer; she is being treated for a "suspicious finding" on the Pap smear. This has been done for over 40 years and is well-accepted by physicians as a preventative approach to borderline Pap smears.

Why couldn't this same approach be used in the case of a suspicious findings on a "probably benign Birads 3 or a suspicious, low-grade Birads 4A reading" after a mammogram, ultrasound, or MRI? These women are currently told, "We are not too sure about this suspicious finding on your structural study" and the radiologist suggests a six-month

recall. The imaging centers also do not give the woman any educational information about what she can do to improve her health in that six-month recall period during which she is now dreadfully concerned. The woman does not want to just wait, she wants to take action to improve her health. My "Proactive Breast Wellness"program/ *Protect Your Breasts* should be offered to These frightened women.

In addition, if the imaging center were to do an infrared thermography on all the suspicious findings cases on structural studies, then the physician would have additional information to help determine if the area is sinister or not. Remember that fibrocysts which are common and lipomas, which are fatty tumors; they both scan "cold" on thermography, which would decrease unnecessary biopsies or procedures. If the infrared instead showed an abnormal TH4 or TH5 thermogram with a hyperthermic focus and blood vessels leading to a palpable mass, then the *Early Freeze Protocol* could be implemented, using cryotherapy to address the suspicious finding. In this case, the woman would not be treated for breast cancer but preventative action would be undertaken on a suspicious finding just like physicians are currently doing for Pap smears and using liquid nitrogen to freeze the woman's cervix.

Ross-Paul and I maintain that if this new "Early Freeze" protocol is used in enough patients, the power of the naturally occurring immune effect will start to show itself, noting that, each time something suspicious is frozen and it was actually a breast cancer, then more than 85 % of those cases will be put into remission.

Cryoablation is breast conserving and the mastectomy rates will drop. Those statistics are easy to track in hospitals. Over time, a statistical base will demonstrate that women treated through early, preventative cryoablation then develop far less breast cancer than those who simply wait, if they continue to engage in early detection combined with cryoablation."

I personally would like to see this clinical trial done and

track the women into the future and see what happens to them over time with continued structural studies and add thermography to their follow up. This is what women want and need!

Cryoablation is obviously inexpensive compared to surgery and results in low morbidity. This should be a win-win for everyone!

Laura Ross-Paul gave our presentation at the Fuda Cancer Hospital in Guangzhou, China, (which used to be called Canton), at the 5th International Cancer Forum on Cryoablation and Stem Cell Research held on July 2, 2016. The forum was organized by the International Society of Cryosurgery, the Asian Society of Cryosurgery, Fuda Cancer Hospital, Jinan University School of Medicine, and the First Affiliated Hospital of Shenzhen University. The organizers had invited over 200 experts and peers from around the world, including America, the U.K., Japan, Australia, and other authorities.

Laura's presentation was well-received by the researchers and her Chinese hosts. My thermography slides were included as part of her presentation to demonstrate pre- and post-cryoablation metabolic tissue response and to promote our ideas about "The Early Freeze Protocol". I was also invited to attend with her, but sadly, I would not have done well on a long 19 hour flight since I am rather claustrophobic.

Ross-Paul said, "I appreciate the forum organizing committee's inclusion of a patient pioneer to speak alongside the doctors and researchers."

This was Laura's second speaking engagement at this forum. The focus of the 2016 forum was on treatment of cancer by cryosurgery, irreversible electroporation (IRE), immunotherapy, and stem cell treatment for cancer.

The "Early Freeze Protocol" is our proposed approach for dealing with "something suspicious" in the breast found through structural studies and thermography.

Please go to the YouTube link to experience for yourself our "Early Freeze" protocol that was presented by Laura Ross-Paul at Fuda Hospital in 2016. You'll find it in my website home page.

If you wish to learn more about the Fuda Hospital programs which at the time of publication of this book, they have satellite offices in the Philippines, Indonesia and Australia. You may contact the hospital directly at Consultation1@FudaHospital.com

Laura's book *They're Mine and I'm Keeping Them* is available through my bookstore. Ross-Paul also maintains a web page at http://keepingthem.com and Facebook site http://Facebook.com/keepingthem.

I also ask that you sign up for my Newsletter link at www.ProtectYourBreasts.com newsletter/ and on my Facebook site https://www.facebook.com/ProactiveBreastWellness/ so that I will be able to keep you up to date on breaking news and research.

I Want You to Get Cryo Equipment For Your Town

Since I first learned about breast cryosurgery in 2010 after scanning Mary prior to her cryosurgery, I knew I had to being this technology to the Pacific Northwest. At the time of publication I have been frustrated because I have been sending my Oregon and Washington breast cancer patients off to California, Arizona and Michigan. In order to speed up the process and to help women find a cryoablation clinic closer to where they live, I have tried a different tact. I want this equipment available if I ever needed it or if my daughter ever had a problem in Seattle. I want my friends and patients to have access to this breast saving technology. So on June 15, 2017, I became the Sanarus Cryoablation Sales Rep for the Pacific Northwest ! Now I can actively try to get this equipment to surrounding towns where the women can access it more easily and not have to fly around the country to get care!

So if you are a woman reading this and you know a radiologist or breast surgeon in your town who you think might consider obtaining cryotherapy equipment, please speak with them and then contact me through my website or at contact@ProactiveBreastWellness.com.

Now I will be given access to a whole library of clinical articles that I can send the physician to review. I feel that within three years this will be the primary option women will want to choose if they have breast cancer or a "Suspicious finding".

I will be calling insurance companies to encourage them to accept and pay for the breast cryoablation CPT code of 19105. At the time of publication no insurance company pays for the code in the Pacific Northwest because there aren't any cryoablation clinics here yet that have asked them to do so! Since Medicare and Blue Cross/Blue Shield, which are national plans, are starting to pay in several states, they may soon reimburse since they will come to see how much money they will save doing cryosurgery vs "Standard of care" !

A Short Synopsis for Prospective Patients from the Sanarus Website

You are probably wondering, what are the parameters that a woman needs to qualify to do cryo. This is a short over view and I council women one-on-one at my clinic, but here is some other information that might prove helpful.

Currently, I suggest to my patients to get all their recent imaging (mammograms, ultrasounds, MRI if (done), imaging reports and biopsy information, (if done) all on a CD from the hospital. I also suggest they ask for a second CD of this material that they hand carry. Since I am sending people around the country right now, the cryosurgery clinic usually wants to review these images and reports prior to you arriving to make sure you may be a good candidate for that center. I have also found that some physicians are bolder than others for what they will treat or the size of the mass etc.

Some of these physicians are in a national clinical study with 20 centers, and they may only do patients that fall into the parameters of the study. Others will treat women on and off the study protocol. This is why it is a good idea that you have your personal information on CD so you can duplicate the CD if you need to send it to a different clinic. I suggest that the women also call the clinic in advance prior to sending CDs, to get costs and other information. It would help if you could go to an active national clinical trial site but that may require travel. As this all moves forward, things will become easier. New technologies sometimes have growing pains, but I think this is just what women have been waiting for!

The Sanarus Visica system is FDA approved to treat cancer and benign tumors in the breast.

Reimbursed using CPT 19105

Over 4000 cases in the U.S. have been done with this equipment.

It is 100% effective for treating early stage breast cancer.

Z1072 study single arm multi-center study in 19 large hospitals by NCI (National Cancer Institute)

100% effective for tumors less than 1cm
92% effective for tumors greater than 1cm. There was some erroneous probe placement so that is why the study states 92%. We actually have 100% ablation in the ablation zone.

These results are highly encouraging given that a lumpectomy is 60 - 80% effective

What you want to know:

Ideal cryoablation candidate

- Lesion size less than or greater 4 cm for Fibroadenomas, and 2 cm for Malignancies
- Your lump needs to be visible by ultrasound.
- 3-5 mm of space between lesion and surface of the breast.
- Patients who are not good candidates for surgery and/or general anesthesia.
- Patients concerned about cosmetics and scaring. Excellent cosmetic effect: one 3 mm incision regardless of tumor size which fades to a freckle size scar over time.
- Patients with anxiety about surgery and general anesthesia.
- The diagnosis must be confirmed by biopsy. (I have been told that some physicians are currently freezing suspicious findings without biopsy).

- **Recommended 3-6 month post-cryoablation follow up visit.**

•Necrotic tissue can show up in mammography until fully resolved so it is important for patient to tell imaging specialists that she has had cryotherapy. Do not allow a biopsy of this area while you are healing. The area will shrink down about 80%.

•Bruising and swelling may occur but will diminish over time.

•Lesion can be potentially palpable for up to a year or more post-cryoablation depending on original size.

•Instructions are similar to a core biopsy, strenuous activities (e.g. jogging, weightlifting, swimming) should be avoided for a brief time.

Remember to sign up on my Newsletter link at
www.ProtectYourBreasts.com newsletter/ and on my Facebook site
https://www.facebook.com/ProactiveBreastWellness/
so that I will be able to keep you up to date on breaking
news and research.

I personally pray that the breast cryoablation or cryotherapy
techniques will be embraced by all surgeons and radiologists
in the very near future. Women are waiting for this
breast-conserving technology that holds such promise.

July 2016

SSO The Society of Surgical Oncology, inc.

Annals of SURGICAL ONCOLOGY

A Phase II Trial Exploring the Success of Cryoablation Therapy in the Treatment of Invasive Breast Carcinoma: Results from ACOSOG (Alliance) Z1072

Rache M. Simmons MD, Karla V. Ballman PhD, Charles Cox MD, Ned Carp MD, Jennifer Sabol MD, Rosa F. Hwang MD, Deanna Attai MD, Michael Sabel MD, David Nathanson MD, Andrew Kenler MD, Linsey Gold MD, Cary Kaufman MD, Linda Han MD, Aaron Bleznak MD, J. Stanley Smith MD, Dennis Holmes MD, Bruno Fornage MD, Carisa Le-Petross MD, Syed Hoda MD, Linda McCall MS, Kelly K. Hunt MD

Breast Oncology
Volume 23, Issue 8 / August , 2016

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Abstract

Background

Cryoablation is a well-established technique to treat fibroadenomas. Pilot studies suggest this could be an effective non-surgical treatment for breast cancer. American College of Surgeons Oncology Group Z1072 is a phase II trial exploring the effectiveness of cryoablation in the treatment of breast cancers.

Methods

The primary endpoint of Z1072 was the rate of complete tumor ablation, defined as no remaining invasive breast cancer (IBC) or ductal carcinoma in situ (DCIS) on pathologic examination of the targeted lesion. A secondary objective was to evaluate the negative predictive value of magnetic resonance imaging (MRI) to determine residual IBC or DCIS. Eligible patients included those

with unifocal invasive ductal breast cancer ≤2 cm, with <25 % intraductal component and tumor enhancement on MRI. A total of 19 centers contributed 99 patients, of which 86 patients (87 breast cancers) were evaluable for data analysis.

Results

Final pathology results, regardless of whether residual IBC/DCIS was in the targeted ablation zone or elsewhere in the breast, showed successful ablation in 66/87 (75.9 %) cancers. The 90 % confidence interval for the estimate of successful cryoablation was 67.1–83.2, with the one-sided lower-sided 90 % CI of 69.0. The negative predictive value of MRI was 81.2 % (90 % CI 71.4–88.8). When multifocal disease outside of the targeted cryoablation zone was not defined as an ablation failure, 80/87 (92 %) of the treated cancers had a successful cryoablation.

Conclusion

Further studies with modifications on the Z1072 protocol could be considered to evaluate the role for cryoablation as a non-surgical treatment of early-stage breast cancer.

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Breast Cancer News announces~Minimally Invasive Breast Cancer Cryotherapy Largely Ignored in U.S., Says Advocate and 13-Year Survivor

March 30, 2016

Laura Ross-Paul and Ingrid Edstrom, FNP, M.Ed. of Proactive Breast Wellness and Infrared Breast Health are attempting to bring cryoablation to the Pacific Northwest in a clinical trial with a radiologist and a breast surgeon. They hope to utilize infrared imaging pre and post cryoablation. Please contact Ingrid at InfraredBreastHealth@gmail.com or call her office to learn more 541-302-2977 PST.

Original Source: Breast Cancer News

Written By: Charles Moore

Date: March 29th, 2016

Laura Ross-Paul of Portland, Oregon, calls herself a "patient pioneer," as one of the first women in the world to receive cryoablation as the primary treatment for her multi-focused breast cancer 13 years ago.

Cryotherapy, also called cryosurgery, cryoablation or targeted cryoablation therapy, is a minimally invasive procedure that uses the application of extremely cold temperatures (cryo) to destroy diseased tissue (ablation), including cancer cells.

For internal tumors, cryotherapy is carried out by using a cryoprobe — a thin hollow wand-like device with a handle or trigger or a series of small needles, attached via tubing to a source of nitrogen or argon, which super-cools the probe tip through which cooled, thermally conductive fluids are circulated. Cryoprobes are inserted into or placed adjacent to diseased tissue in a way that ablation will provide correction, yielding benefit to the patient.

The cryoprobe is placed in the proper position using imaging guidance, and as internal tissue is being frozen, the physician avoids damaging healthy tissue by viewing movement of the probe on ultrasound, computed tomography (CT) or magnetic resonance (MRI) images transmitted to a video monitor. With the probes in place, the cryogenic freezing unit removes heat from the tip of the probe and by extension from surrounding tissues.

Ablation occurs in tissue that has been frozen by at least three mechanisms:
• Formation of ice crystals within cells, thereby disrupting membranes and interrupting cellular metabolism among other processes;
• Coagulation of blood thereby, interrupting blood flow to the tissue, in turn causing ischemia and cell death;
• Induction of the so-called programmed cell death cascade.

Ross-Paul received her cryotherapy treatment in 2003 at the Karmanos Cancer Center in midtown Detroit, Michigan, one of 41 National Cancer Institute-designated Comprehensive Cancer Centers in the U.S. and the only hospital in Michigan dedicated exclusively to fighting cancer.

With continuing improvement of imaging techniques and development of devices that can more precisely control the topical application of extreme temperatures to better control extreme temperatures, Karmanos Cancer Center physicians use cryotherapy as a treatment for patients with skin tumors, precancerous skin moles, nodules, skin tags, or unsightly freckles. They can also use cryotherapy to treat patients with benign and malignant breast tumors, although cryotherapy to treat malignant breast tumors is still considered experimental, and certain other cancers, including cancers of the prostate, liver (usually metastasized from other organs), cervix, and fibroadenoma.

Cryotherapy Benefits

Compared with other techniques, one of the benefits of cryotherapy includes minimal pain, minimal scarring, lower cost, and faster recovery times. The Karmanos Cancer Center, which is affiliated with Wayne State University's School of Medicine, explains that once diseased cells are destroyed, components of the immune system clear out the dead tissue, and that patients undergoing cryosurgery usually experience minor to moderate localized pain and redness, which can be alleviated by over the counter painkillers such as aspirin or ibuprofen, and application of topical steroid creams.

Blisters may form, but they usually scab over and peel away. As with any medical treatment, there are risks involved, primarily damage to nearby healthy tissue and the potential for not thoroughly freezing the entire tumor during treatment. Damage to nerve tissue is also of particular concern.

Now a cryotherapy activist and advocate, Ross-Paul says that while to date there have been several dozen patients treated by cryoablation for breast tumors by Dr. Peter Littrup, a pioneer in the cryotherapy field, the Chinese, who began using cryoablation to treat breast cancer about the same time as Littrup, have treated more than 3,800 women using the method.

"Disturbing"

"The fact that these tremendous advances in China have not been duplicated in the U.S. is disturbing," Ross-Paul said. "As activists promoting cryoablation in America, I and my husband have tried to identify why the progress in America is so slow, and then conceive of a solution to this problem. We believe we have the answer."

Ross-Paul contends that "in America, cryoablation is seen as a treatment that needs to be proven effective before it is considered a safe alternative to the mastectomy and lumpectomy. FDA trials have been undertaken in the last 13 years, but the size of the trials have been limited due to financial constraints. As a result, when a doctor advises their patient who has breast cancer, cryoablation is considered as an unproven, experimental alternative to the much safer and statistically proven surgery."

"Without statistical proof through trials," she said, "cryoablation wont be used. But if cryoablation isn't used, there will be no statistics. This has doomed cryoablation in the U.S. to forever be an experimental treatment. To get around this dilemma, we believe that prevention is the key. Through early detection, women are finding something suspicious in a mammogram. Since it is not yet identified as cancer, they are told to wait and see if it develops. If it doesn't, after a long time of fearful waiting, there is a joyful sigh of relief. If it is cancer, however, at that point, cryoablation is not considered and only surgery is advised."

What Women Want

But "women don't want to just wait and do nothing," Ross-Paul said. "In this six month wait-and-see period they are ready for action. The solution is to develop a new protocol that accompanies early detection, and that would be to use cryoablation to freeze anything suspicious. Why wait for something to manifest as a tumor? Why not keep the patients' safety uppermost in mind and ablate the unusual tissue, and then follow up with more imaging? Cryoablation can't hurt the breast, it is almost painless and very inexpensive. And if something suspicious returns, use cryoablation again until the condition either goes away, or becomes an obvious tumor which can then be treated by cryoablation, or by surgery."

Ross-Paul maintains that if this new protocol is used in enough patients, the power of the naturally occurring immune effect will start to show itself, noting that "each time something suspicious is frozen and it was actually breast cancer, then about half those cases will be put into remission. Over time, a statistical base will demonstrate that women treated through early, preventative cryoablation develop far less breast cancer than those who simply wait, if they continue to engage in early detection combined with cryoablation."

“There is no need to prove that cryoablation is superior to or as effective as surgery,” Ross-Paul said, “although efforts to do so can and should continue on a separate track. It can prove itself through this new protocol by eventually reducing the incidence of breast cancer almost entirely. This is what women need. This is what women want.”

 Ross-Paul has co-written a book with her husband, Alex Paul, and her cancer physician, Dr. Peter Littrup, titled “They’re Mine and I’m Keeping Them,” which documents the story of how she and her husband bucked the system and found Littrup, whose  advanced skill in the field of cryo-ablation ultimately saved her breast. The co-authors also relate the success at Fuda Hospital in Guangzhou, China in treating a variety of Stage 4 cancers by combining cryoablation and advanced immune system therapies, which increase the frequency of the occurrence of the natural immune effect to approximately 80 percent or higher of the cases.

“They’re Mine and I’m Keeping Them” is available from Amazon.com in both hard copy and ebook (Kindle) versions. Ross-Paul also maintains a Web page: http://keepingthem.com and a Facebook site:http://Facebook.com/keepingthem.

Through her several avenues of outreach, Ross-Paul says she has helped a handful of women receive cryoablation treatment by Littrup, and “has learned that women need a cure for cancer,

and they want that cure to not involve losing their breast through a mastectomy or disfiguring it with a lumpectomy."

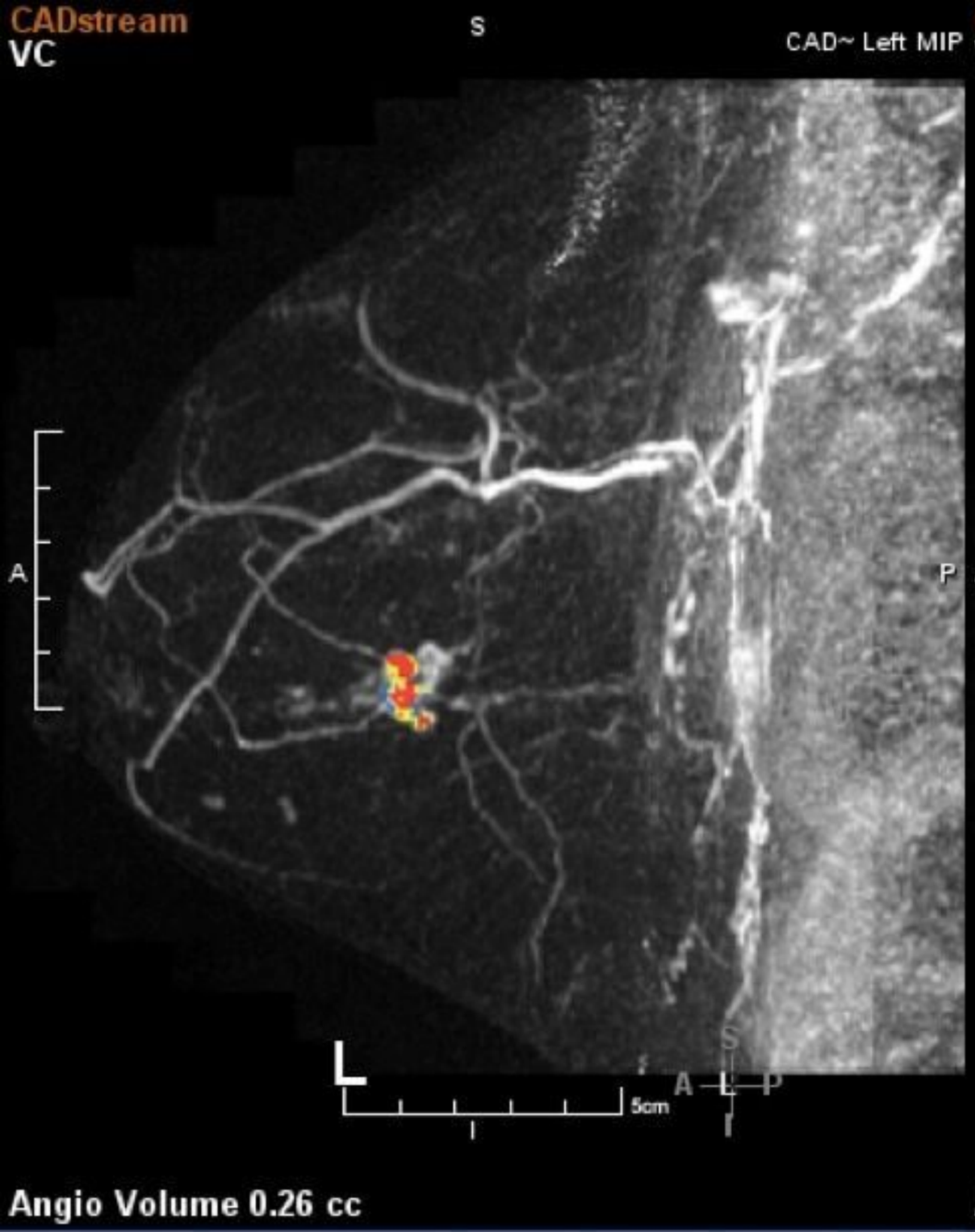
She said that "while a cure for breast cancer might someday achieve these goals through the simple action of taking a pill, that day has not yet come," and that "in the meantime, cryoablation can put breast cancer in remission, giving women what they need, and not disfigur[ing] a woman's breast, thus giving women what they want."

"The beauty of cryoablation," Ross-Paul said, "is that it is breast conserving — I was able to avoid a mastectomy," its low morbidity — "I never needed more than a Tylenol," and its inexpensive cost compared to surgery. Ross-Paul says another major benefit of cryoablation is that in about half of all cases, "cryoablation naturally stimulates the body's immune system to develop an immunity to the cancer as it eats up the now-dead tumors."

Ross-Paul has recently been asked to speak at the 5th International Forum on Cancer Treatment to be held July 1-3 in Guangzhou, China, which will be her second speaking engagement at this forum. The focus of the 2016 forum will be on treatment of cancer by cryosurgery, irreversible electroporation (IRE), immunotherapy, and stem cell treatment for cancer.

The forum is organized by the International Society of Cryosurgery and Asian Society of Cryosurgery, Fuda Cancer Hospital, Jinan University School of Medicine, and the First Affiliated Hospital of Shenzhen University. The organizers have invited experts and peers from around the world, including America, the U.K., Japan, Australia, and other authorities.

"I appreciate the forum organizing committee's inclusion of a patient pioneer to speak alongside the doctors and researchers," Ross-Paul said.



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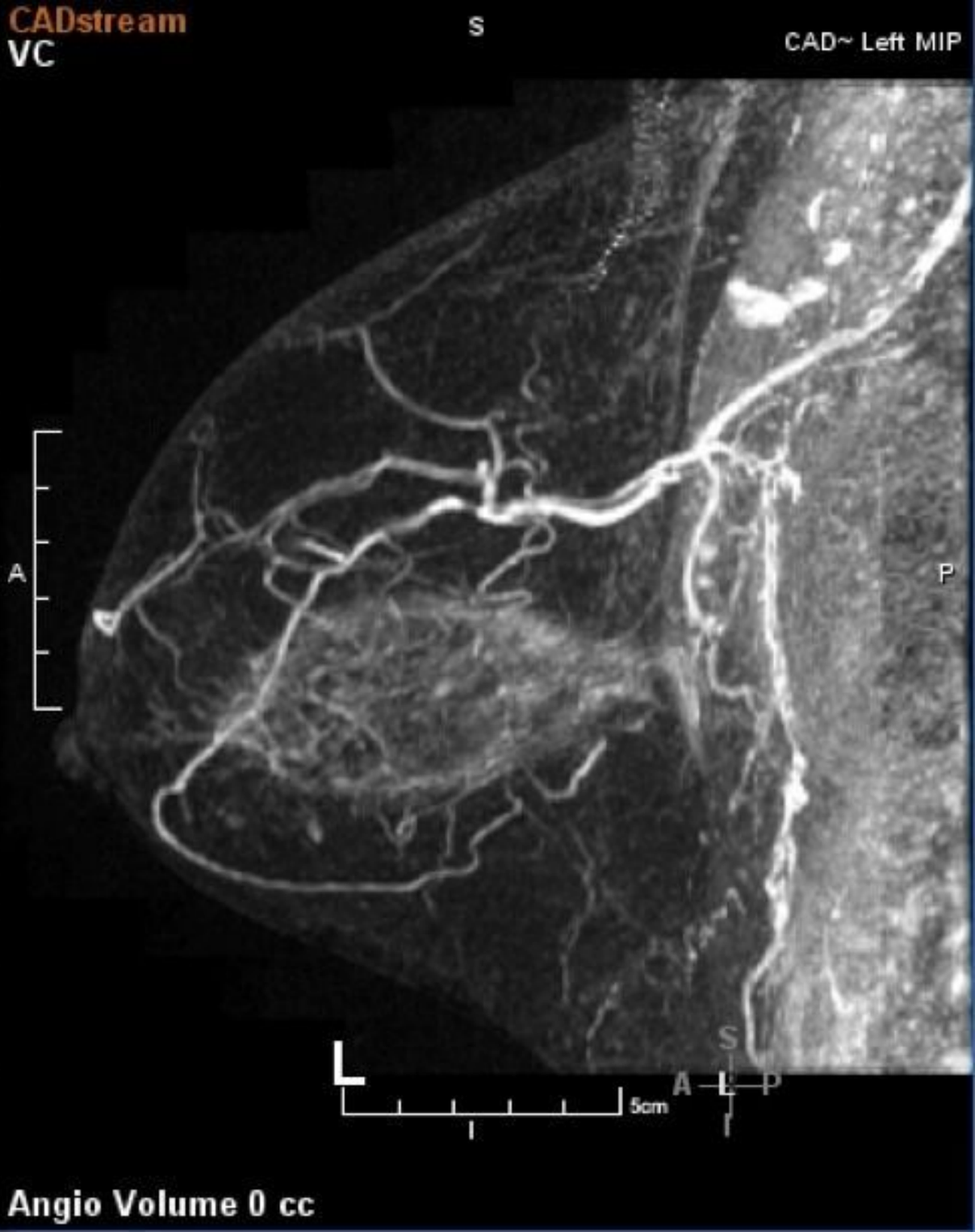

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Cryotherapy for Breast Fibroadenomas[1]

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PURPOSE: To assess freezing protocols, imaging, and clinical outcomes of percutaneous ultrasonographically (US)-guided cryotherapy for breast fibroadenomas.

MATERIALS AND METHODS: Institutional review board approval and patient consent were obtained. Forty-two biopsy-confirmed fibroadenomas were treated in 29 patients (mean age, 27 years) by using a 2.4-mm cryoprobe inserted into the fibroadenoma with US guidance. The first seven patients underwent conscious sedation, but the other 22 patients required only local anesthesia. US and thermocouple monitoring of the procedure were performed to evaluate freeze protocols based on tumor size. Saline injections protected the skin and/or chest wall. US follow-up was performed at 1 week and at 1, 3, 6, and 12 months. Pre- and 12-month postcryotherapy mammograms were available for seven patients who were over 30 years old. χ^2 and Student t tests were used to assess frequency and mean differences, respectively.

RESULTS: The 22 patients who underwent local anesthesia reported minimal discomfort. No significant complications were noted, and patients were very pleased with the resolution of palpable mass effect and cosmetic results. The average pretreatment fibroadenoma volume of 4.2 $cm^3 \pm$ 4.7 (standard deviation) was reduced to 0.7 $cm^3 \pm$ 0.8 at 12-month follow-up (73% reduction, $P < .001$). US produced excellent ice visualization beyond tumor margins, while thermocouples confirmed cytotoxic temperatures approximately 5 mm behind the visible leading edge. Two patients elected to undergo either removal or biopsy of a residual mass, which revealed a shrunken hyaline matrix with preserved collagenous architecture. Mammograms showed comparable resolution of mass effects with mild surrounding parenchymal reaction.

CONCLUSION: Cryotherapy of fibroadenomas is a safe, effective, and virtually painless clinic-based (ie, outpatient) treatment option with good cosmesis.

Nonsurgical treatments for benign breast masses have clinical goals of stopping growth and/or reducing (removing) palpable mass effect without leaving a surgical scar (ie, good cosmesis). If cryotherapy could accomplish these goals, substantial psychologic and economic benefits could be realized for many of the 1.3 million women who undergo breast biopsy each year in the United States (1). Despite the increasing use of confirmatory needle biopsy, an estimated 500 000 fibroadenomas are still surgically excised (2,3). Factors that may lead patients to choose removal of a benign mass include palpable prominence, localized discomfort, interval growth, and peace of mind. For certain patient groups, multiple growing masses are more problematic. Fibroadenomas in African American women occur at a younger age, are more commonly multiple, and overall have twice the incidence of those seen in white women (4–7).

Resection has been the standard, but nonsurgical options for benign or malignant breast masses include vacuum-assisted biopsy (8,9), radiofrequency ablation (10,11), laser therapy (12), and cryotherapy (2,3,13,14). Newer 8-gauge vacuum-assisted biopsy devices may achieve visual removal for some masses up to 2 cm in maximal diameter, but complete resection may still be limited by targeting and/or visualization difficulties due to local hemorrhage as multiple cores are obtained (9). Heat-based treatments are difficult to monitor with ultrasonography (US) and are limited by potential skin damage if masses are less than 1 cm from the chest wall or skin surface (11). Cryotherapy is easily visualized with

high-frequency (ie, high-spatial-resolution) US as the ice margin extends beyond the tumor, is virtually painless, and can be used for masses near the skin. In this article we describe the experience of the single institution with the largest cohort and focus on its unique detailed imaging database, which was not covered in the article from the multicenter trial (2,3), and share some insights from our patient population. The purpose of our study was to assess freezing protocols, imaging, and clinical outcomes of percutaneous US-guided cryotherapy for breast fibroadenomas.

MATERIALS AND METHODS

Patients

Procedures were performed under an instutional review board–approved protocol as part of a multicenter prospective trial. An informed consent form for the trial was also approved by our institutional review board and was thoroughly discussed with and signed by all patients. This report is limited to the institution at which more than 50% of cases in that trial were performed (2,3), with collection of detailed imaging aspects of freeze monitoring and evaluation over time. Prior to cryotherapy, large-core needle biopsy was performed to confirm the diagnosis of 42 fibroadenomas in 29 patients. All biopsy and cryotherapy procedures were performed by a radiologist (P.J.L.) with approximately 10 years of interventional and breast imaging experience. The consecutive patients who met our study criteria were newly diagnosed, had growing fibroadenomas or palpable discomfort, and were offered resection in all cases. A growing fibroadenoma was defined by an increase in at least two of three dimensions on breast US images. Age and race were assessed in relation to outcomes. The first seven procedures were performed as ambulatory surgery and made use of intravenous sedation. It quickly became apparent that an office (outpatient) setting and local anesthesia without sedation were more appropriate for the procedure, so all subsequent cases were performed in such a manner.

Equipment and Cryotherapy Protocols

Real-time US guidance was used to document fibroadenoma sizes and to guide thermocouple and probe placements, as well as to monitor iceball formation and associated safety measures (ie, sterile saline injections). US monitoring (model 9000; GE Medical Systems, Milwaukee, Wis) was performed (P.L.L., approximately 10 years of experience in US guidance) with a high-frequency (10–13 MHz) linear-array probe. Each fibroadenoma was characterized with respect to its general location within the breast (ie, quadrant) and its width, height, and length. Note was also made of tumor blood supply by using power Doppler estimates of internal, or "feeder," vascularity.

During the freeze cycles, the maximal transverse dimension of the iceball was recorded for each minute of the freeze and refreeze cycles. Longitudinal iceball measurements do not change significantly during freezes along the 4-cm exposed tip; therefore, overall ice lengths were consistently 5–6 cm for all freezes. The iceball size at the initiation of the second freeze was back-calculated by using the stable rates of iceball progression (in centimeters per minute). A disposable 2.4-mm–diameter air-gap–insulated cryoablation probe (Visica Treatment System; Sanarus Medical, Pleasanton, Calif) was used for all masses. In 10 cases, a multiple port system (Cryocare; Endocare, Irvine, Calif) was used so that two probes could be used simultaneously, as follows: In nine patients, two masses were treated at the same time, and in one patient, two probes were used to cover a larger discoid mass ($3.9 \times 3.9 \times 1.3$ cm) for which the long axis of the cryoablation probe simply could not be chosen for the greatest fibroadenoma measurement. Freezing at the distal end of the cryoprobe occurred according to the Joule-Thompson effect, in which argon gas is decompressed by more than 2000 psi (14 000 kPa) within the closed tip of the probe, reaching temperatures approaching that of liquid argon (−187°C).

The Visica Treatment System and Cryocare units have adjustable duty cycles, which can be used to alter the length of time that argon gas expands to cool the probe. At "100% duty cycle" argon flows continuously, while at "10% duty cycle" argon flows for 1 second and is stopped for 9 seconds of every 10-second period. We decided that protocol freeze parameters needed to be altered after our first case, in which we used a 100% freeze for 10 minutes, followed by a 10-minute thaw and another 10-minute 100% freeze. The resultant iceball dimensions ($3.5 \times 3.5 \times 5.5$ cm) were considered too destructive for the surrounding normal tissue in the treatment of most benign tumors (ie, <2 cm in average diameter). A balance of sufficient freeze time and intensity was standardized according to the size of fibroadenomas, which were grouped by 1-cm increments up to 4 cm, at all investigational sites (2,3). The freeze times were selected according to the algorithm to accommodate the greatest dimension of fibroadenoma sizes for each of four maximum tumor diameter ranges (protocols 1–4: 0–1.0 cm, 1.1–2.0 cm, 2.1–3.0 cm, and 3.1–4.0 cm, respectively) within the relatively insulating (ie, fatty) breast tissues. The problem of inadequate treatment was prevented by limiting maximal fibroadenoma dimension to 4 cm, which also helped avoid the problem of phyllodes tumors, which are rarely smaller than 4 cm (2–6). In addition, if thorough coverage by toxic ice (ie, <−40°C) is achieved, even locally aggressive higher-Gleason-score prostate tumors have shown potentially better long-term outcomes than has surgery or radiation therapy (14).

At our investigational site, we also elected to obtain thermocouple documentation of cytotoxic temperature margins within the breast tissues. For all tumors 1 cm in diameter or larger, each 100% duty cycle freeze was followed by a maintenance freeze at 10% duty cycle; this process was designed to maintain cold temperatures within the tumor while slowing the expansion of the iceball beyond its borders. Osmotic shifts take place during thawing (15,16), which sensitize cells for greater cytotoxicity during the second freeze. Therefore, a freeze-thaw-freeze technique was used in all cases. The passive thaw between the first and second freeze was continued until the probe warmed to about −1°C. Typically, the time required for such warming was about the same as the total time of each freeze.

Procedure

The patients were prepped and draped in sterile fashion. The angle of approach was chosen along the longest axis of the fibroadenoma to use the longer freeze length of the cryoprobe. A lateral or inferior puncture site was selected when possible for best cosmetic results. The overlying skin was infiltrated with buffered 2% lidocaine and was extended around all tumor margins. After a 3-mm skin nick was made, a 12-gauge coaxial trocar needle (Bard, Covington, Ga) was advanced through the center of the fibroadenoma. Transverse US scanning (Fig 1a) allowed us to verify central placement. Once the trocar needle tip penetrated the distal margin of the mass (Fig 1b), the stylet was removed and was replaced with the 2.4-mm cryoprobe. The needle sheath was then retracted to ex-

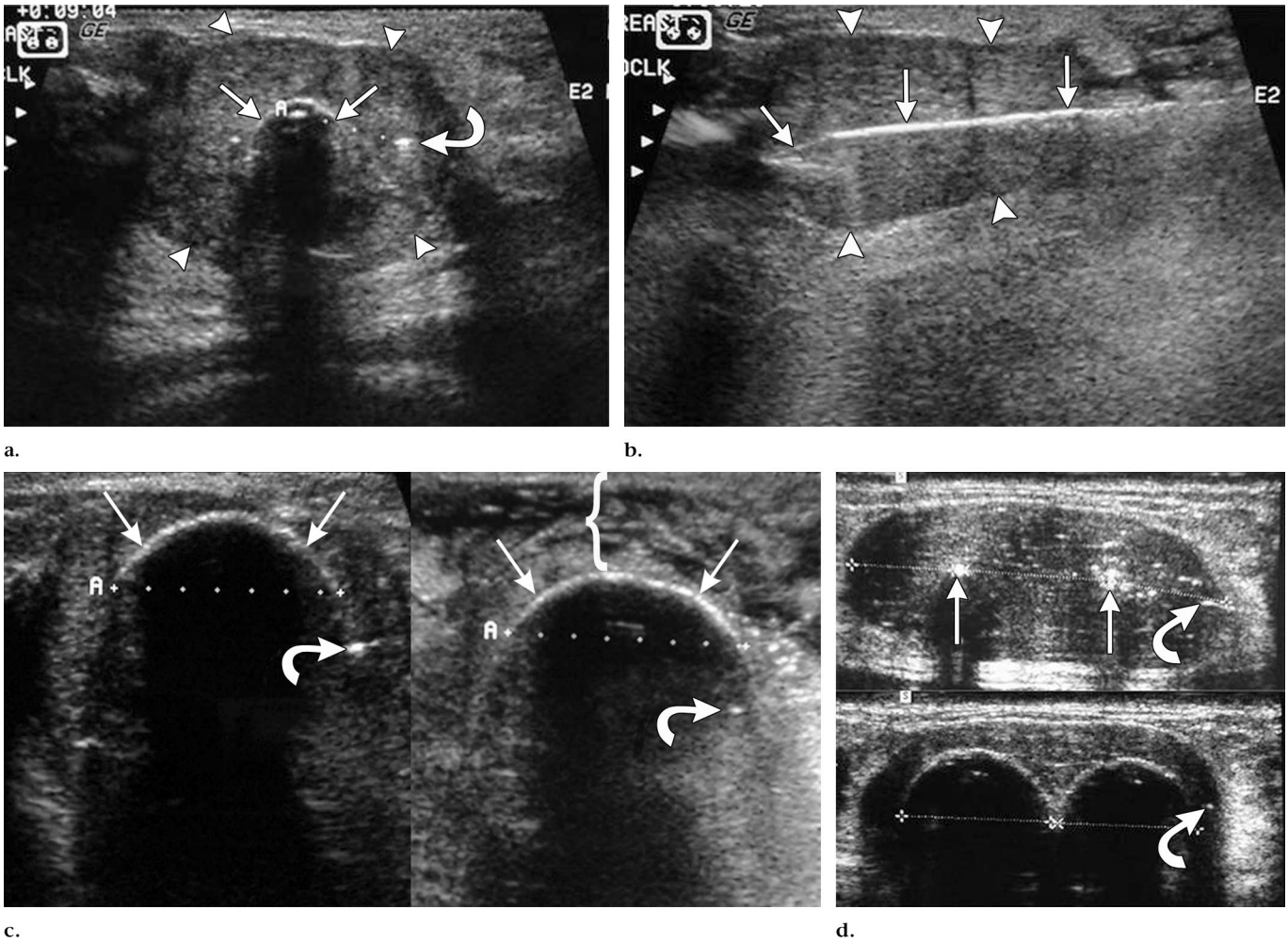
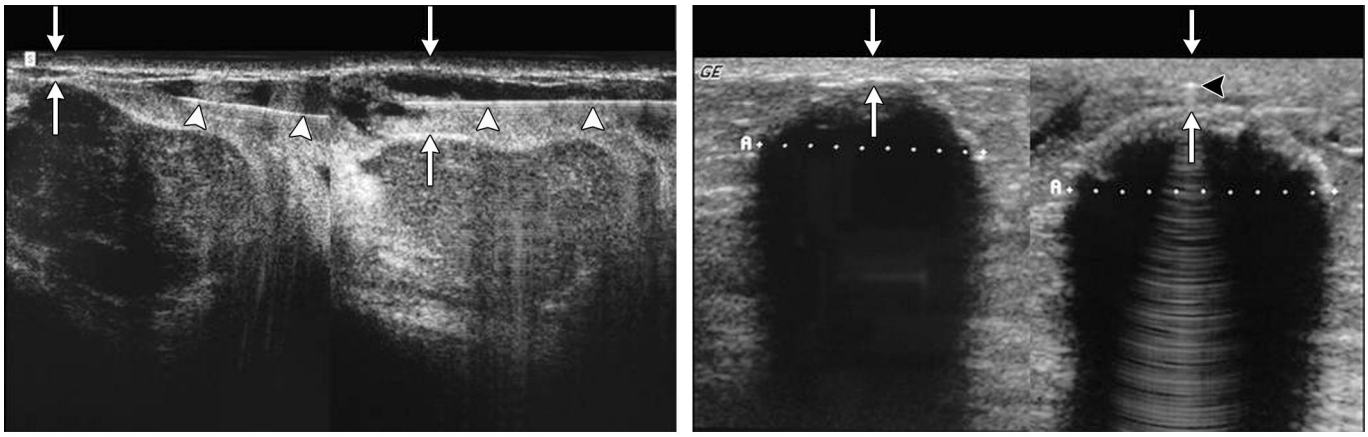


Figure 1. US images. **(a)** Transverse view of developing iceball (<1 cm in diameter; straight arrows) in 2.3-cm-diameter fibroadenoma (arrowheads) at initiation of freeze. Thermocouple tip (curved arrow) is 7 mm from the cryoprobe. **(b)** Longitudinal view of fibroadenoma (arrowheads) with a 12-gauge trocar placement needle (arrows) prior to removal of the stylet and replacement with the cryoprobe. **(c)** Transverse view of growing iceball (straight arrows) at 2 (left) and 3 (right) minutes, and thermocouple (curved arrow) is just becoming engulfed in ice at 6°C and −6°C, respectively. At 3 minutes, note the thickened skin distance (bracket) due to interval saline injection. **(d)** Transverse view of a large unusually shaped (ie, discoid, not cylindrical) fibroadenoma with cryoprobes (straight arrows) in place (top) and growing ice at 1 minute (bottom). The thermocouple (curved arrow) is about to be engulfed in ice. The iceball subsequently fused to create a smooth discoid shape, which was only possible with the probes placed less than 1.5 cm apart and approximately 1 cm from the fibroadenoma margin.

pose the distal 4 cm of the cryoprobe. The coaxial sheath also helped insulate the insertion tract from freezing damage. The system was then briefly activated at 10% duty cycle to "stick freeze" the probe in place, while a thermocouple was placed through an 18-gauge arterial needle. The thermocouple tip was lodged beneath the outer rim of the fibroadenoma, which prevented it from subsequently being pushed laterally by the advancing iceball in the loose breast fat (Fig 1c, 1d). Thermocouple distance from the cryoprobe varied between 4 and 12 mm, depending on the fibroadenoma diameter and the depth of insertion of the thermocouple beneath the capsule. Temperatures from thermocouples within the fibroadenoma and along the skin surface were recorded at 1-minute increments throughout the procedure.

At the time of this trial, cryoprobes had air-gap insulation and allowed freezing temperatures to propagate up the probe shaft. Skin protection at the cryoprobe insertion site included the dripping of sterile room-temperature saline on the skin and the placement of moist gauze between the probe (or sheath) and the skin. US-guided sterile saline injections (range, 10–40 mL) were used between the iceball and the skin surface (Fig 2) or chest wall, when needed, throughout both freeze cycles to keep the advancing ice at least 5 mm from either surface. In later patients (ie, later in consecutive enrollement), saline injection was not necessary between the iceball and chest wall as long as gentle to-and-fro movement of the iceball within the breast was maintained. This motion prevented ice from propagating posteriorly but needed to be initiated before the ice margin came close to the pectoralis muscle.

Switching from argon to helium gas by means of the thaw switch on the systems actively warmed the probe after the final freeze cycle. This "active thawing" phenomenon facilitated prompt removal (ie, <2 min) of the probe from the iceball. Manual pressure was then applied for at least 20 minutes to decrease the risk of hematoma formation. Patients were discharged home with a pain scale question-



a. **b.**

Figure 2. **(a)** Longitudinal and **(b)** transverse US views show progress of saline injection. The needle (arrowheads) is increasing the distance (arrows) from the skin surface to the fibroadenoma, from less than 3 mm (left image in both **a** and **b**) to more than 8 mm (right image in both **a** and **b**).

naire to monitor any discomfort. A standard visual analog pain scale (ie, score of 0–10, corresponding to a spectrum of facial expressions from happy [score of 0] to crying [score of 10]) was used. Patients were seen at follow-up at 1 and 6 weeks and at 3, 6, and 12 months after cryotherapy in our comprehensive breast center.

At follow-up, patient satisfaction, tumor palpability, and clinical appearances were evaluated by a single nurse practitioner (L.F.G.) with approximately 10 years of dedicated breast care experience at our center. She monitored overall patient well-being (eg, constitution, affect), as well as palpably measured mass effect (ie, estimate of outer fibroadenoma margins in centimeters) and clinical appearance related to skin appearance and/or scarring. All US images and available mammograms ($n = 7$) were evaluated by an experienced breast imager (P.J.L.). Margins of treatment effect in adjacent tissues and the underlying fibroadenoma were both measured on US images, and the overall appearance (eg, cystic component, vascular flow) was noted. Since the number of follow-up mammograms was too limited for any significant analysis, overall appearance (ie, visibility and/or size of fibroadenoma mass effect and density of surrounding parenchyma) was noted. Three patients underwent follow-up biopsy because of their concern and/or dissatisfaction about persistent or perceived increase in palpable mass effect. Specimens were evaluated by a pathologist (W.S.) with approximately 15 years of breast pathology expertise.

Statistical Analysis

Assessment was limited to observational differences and was not intended to power the sample size of the study. The two-tailed Student *t* test was used for all mean value comparisons. The χ^2 test was used for frequency comparisons (ie, percentages). A significant difference was declared at $P < .05$. Analyses were performed by the lead author (P.J.L.) by using calculated fields on a standard spreadsheet (Excel; Microsoft, Redmond, Wash) and were validated by the sponsoring company (Sanarus Medical).

RESULTS

Twenty-nine patients underwent cryoablation of 42 fibroadenomas. Nine patients had two fibroadenomas treated in one session and 19 had a single fibroadenoma treated. One 15-year-old white patient who had undergone four previous resections and had associated keloid scarring underwent three cryotherapy sessions for five new fibroadenomas treated within this protocol, and the sessions were performed approximately 3 months apart. She also had two additional fibroadenomas treated off-protocol (ie, not included in this study) following U.S. Food and Drug Administration approval of the procedure and coverage by her insurance. African American patients comprised the majority of the study group (16 of 27, 60%). Patient age ranged from 13 to 50 years (mean, 26.6 years); African American ($n = 16$) and non–African American ($n = 11$) patients had mean ages of 24.6 years ± 11.9 (± standard deviation) and 29.0 years ± 11.9, respectively. There was no statistically significant difference in the mean age by race nor was there any significant racial predilection for other outcome parameters ($P > .05$). A total of 37 fibroadenomas had at least 1 year of follow-up. Because of the young age of most patients, only seven women (over 30 years of age) underwent pre- and postprocedure mammography. Patient-reported pain on the visual analog scale averaged a score of only 1 (out of 10) during the first week, then pain resolved. The average pretreatment fibroadenoma volume of 4.2 cm^3± 4.7 was markedly reduced to 0.7 cm^3± 0.8 at 12 months (73% reduction, $P < .001$).

US and Temperature Monitoring

Rapid iceball growth occurred with the initial 100% duty cycle at an estimated rate of 1.2 cm/min for the first minute and then slowed to approximately 0.3 cm/min for the next 3 minutes for all protocols (Fig 3). The 10% "maintenance" freeze slowed the rate of iceball expansion to less than 0.1 cm/min. During the thaw phase, the iceball diameter reduced approximately 7–8 mm in all protocols. During the second freeze, progression of iceball size during the 100% duty cycle was approximately 0.4 cm/min for protocol 2 but was only 0.15 cm/min for protocols 3 and 4. Slowing of the iceball progression at 10% duty cycle in the second freeze (0.075 cm/min) occurred promptly for protocol 2 but appeared delayed by 1 and 2 minutes for

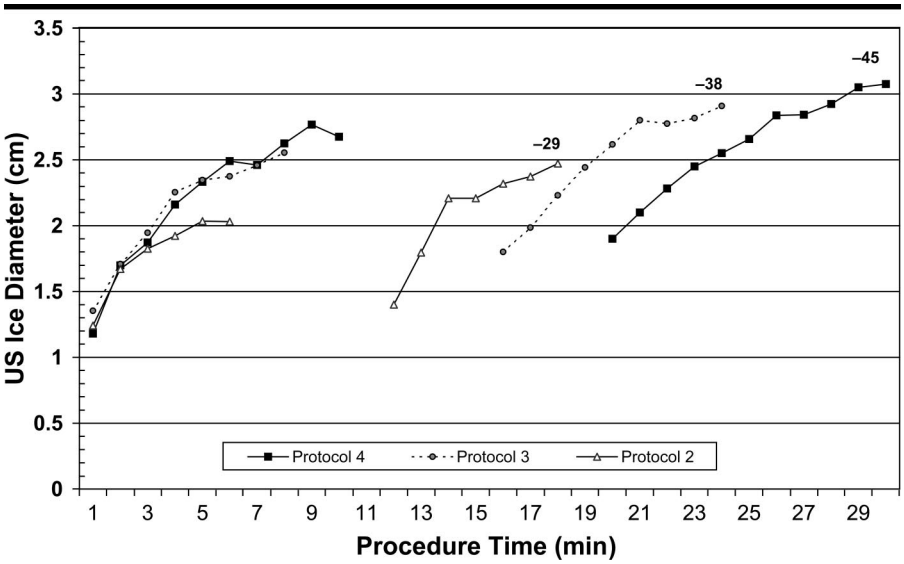


Figure 3. Graph shows transverse iceball dimensions over time for three freeze protocols, as well as lowest mean temperature attained at completion of second freeze. The two sets of ice growth curves correspond to the freeze portions with intervening thaw, which shows that small tumors were treated within about 18 minutes whereas the largest tumors took about 30 minutes total. *Protocol 2* (1.1–2.0-cm fibroadenoma) = 2 minutes at 100%, 4 minutes at 10%; *Protocol 3* (2.1–3.0-cm fibroadenoma) = 4 minutes at 100%, 4 minutes at 10%; *Protocol 4* (>3-cm fibroadenoma) = 4 minutes at 100%, 6 minutes at 10%.

protocols 3 and 4, respectively. The second freeze cycle expanded the freeze rim approximately 5 mm beyond the greatest extent achieved at the conclusion of the first freeze for all protocols. At the end of the second freeze, no differences in mean iceball diameter were noted between protocols 2 and 3 (approximately 2.0 vs 2.4 cm, respectively; $P < .05$) than between protocols 3 and 4 (approximately 2.4 vs 2.6 cm).

Cytotoxic tissue temperatures (<−20°C) were noted at the periphery of the iceball at the completion of the second freeze for all protocols. Average final temperatures were used to avoid inherent measurement errors with thermocouple placements and their associated variable distances from the cryoprobe. Lower temperatures were noted for longer freeze times, which suggests that while the iceball may not grow significantly after a stabilization phase, the cytotoxic isotherm continues to move closer to the visualized ice margin over time. From these observations, a uniformly cytotoxic temperature of less than −40°C (14–16) appeared to lay approximately 5 mm behind the leading edge of the visualized iceball at the second freeze. Total procedure times were not specifically measured, but Figure 3 confirms that the actual total time for freezing cycles and probe removal is less than 30 minutes.

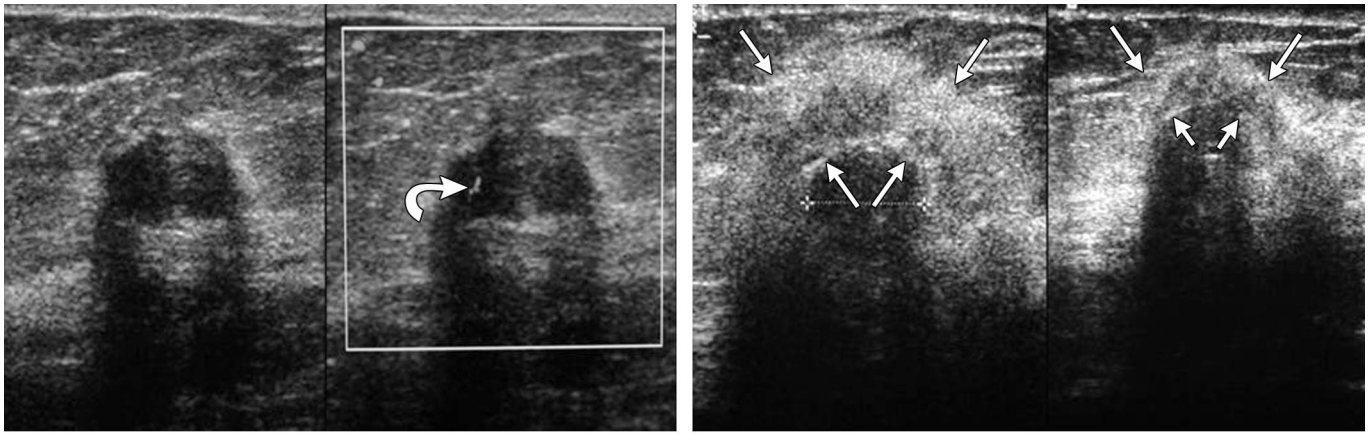
Follow-up Imaging and Clinical and Pathologic Evaluation

The change in US appearance over time provided both qualitative and quantitative information about the healing phases of breast cryoablation. By the end of the second freeze, ice margins extended beyond the fibroadenoma margins in all patients. This was substantiated by noting the evolving US appearance of the fibroadenoma and adjacent breast tissue during follow-up (Fig 4). Color Doppler flow was not seen within the treatment zone but appeared more intense immediately beyond the echogenic cryoablation margin during the first week after ablation. Color Doppler evaluation at later follow-up still showed no significant flow in the cryoablation zone and showed more normalized flow in adjacent tissue. After 3 months, differentiation of the ablated fibroadenoma from the surrounding treated area at US became more difficult in some patients. At 6 months, four fibroadenomas showed some fragmentation, one of which had a cystic component. At 12 months, continued shrinkage occurred to the point that five of the fibroadenomas could no longer be identified, and 10 were reduced by more than 90% in volume.

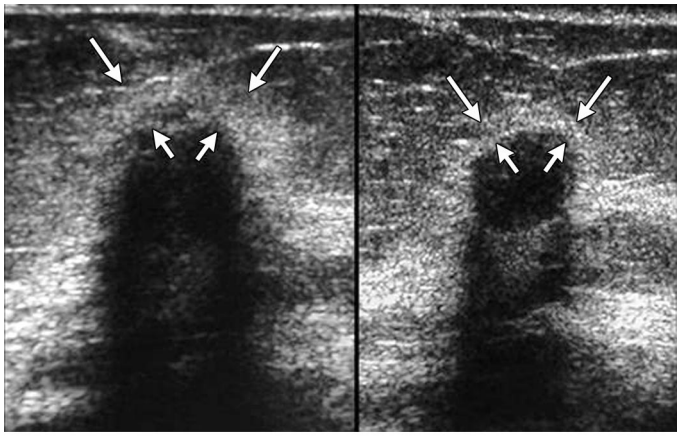
A potentially aberrant healing reaction in the surrounding parenchyma occurred in three younger patients and was therefore seen only at US (Fig 5). At 6 months, a palpably soft but larger area was noted at physical examination and US of the treatment site. The region had overall echotexture similar to that of hypoechoic breast fat, including subtle structural bands. While no significant color Doppler flow was noted in the central fibroadenoma scar, normal color Doppler flow was noted within this surrounding region. One patient elected to continue conservative observation with US. One patient elected to undergo resection of the whole area, and another underwent large-core needle biopsy of the peripheral and central areas. Histologic results are available from these two cases of periablation tissue reaction (Fig 5), as well as from the single case in which a patient requested excision for suboptimal tumor volume reduction, despite a decrease from 2.0 to 0.7 cm^3 (70% reduction). In all three of these cases, histologic results from the fibroadenoma scar revealed extremely hypocellular or acellular collagenized stroma with very few or absent epithelial components. The two excision specimens demonstrated close size correlation with that seen on the US image of the shrunken scar (Fig 5d). In all three cases, peripheral histologic evaluation revealed normal breast tissue (Fig 5c). In the case of the dissatisfied patient, the peripheral breast tissue had some areas of fibrosis. Her preprocedural core biopsy had also demonstrated a more fibrotic and less cellular tumor.

Follow-up mammograms were available only for the seven patients older than 30 years. These mammograms had an appearance similar to that of the final US pattern (Fig 6), but some were difficult to explain; namely, in patients who had a minimal discernible nodule at mammography, one had a distinct smaller mass at US (Fig 6, *A*), while another had residual ill-defined changes at US (Fig 6, *B*). Two of the patients had a slightly larger area of asymmetric density remaining in that area, one of whom was the patient who had cystic degeneration (Fig 6, *C*).

Among the patients who had a palpable mass prior to treatment of their fibroadenomas (95%, 40 of 42), 12-month follow-up questionnaire data were available regarding 37 fibroadenomas. Of these, 89% (33 of 37) had palpably resolved or were substantially less noticeable to the patient by 12 months after the procedure. Patients and health care providers were very satisfied with the cosmetic outcomes. No apparent skin alteration over the iceball site was noted. There were no cases of "volume reduction" skin depres-



a. b.



c.

Figure 4. Transverse US images of a fibroadenoma. **(a)** Image with power Doppler view (right) shows only a small amount of internal flow (arrow), common for growing fibroadenomas in our series. **(b)** Images show cryotherapy site at 1 month (left) and 3 months (right) later. Decreasing thickness of adjacent echogenic breast tissue (arrows) most likely corresponds to resolving edematous and/or inflammatory reaction and/or necrosis surrounding the shadowing central fibroadenoma. **(c)** Images show cryotherapy site at 6 (left) and 12 (right) months later. The presumed peripheral organizing necrosis continues to resolve (arrows), as does the central fibroadenoma (decrease of 70%).

sion that can accompany open surgical excision. Scarring at the probe insertion site ranged from complete healing (ie, clinically undetectable) to some hypopigmentation of up to 1.5 cm in three African American patients at 3 months. However, the hypopigmentation resolved at between 6 and 12 months and was attributed to the air-gap–insulated probe. The greatest skin effects were related to different surgical tapes used with the covering gauze pads. Later patients were given only a bandage after the 20-minute compression and were told to place gauze over the bandage and beneath a supportive brassiere to manage any minor immediate oozing. Only one African American patient had a 5-mm hypertrophied scar, or minor keloid formation, at a cryoprobe insertion site. All patients were offered the opportunity to undergo resection of any residual fibroadenoma if they were displeased with the outcome. To date, only two patients have elected to undergo resection (one for a persistent palpable nodule, the other for the previously noted periablational tissue reaction). Several patients displayed their satisfaction by undergoing repeat cryoablation for other fibroadenomas off protocol, once the cryoablation system was approved by the Food and Drug Administration for that indication and became commercially available.

DISCUSSION

Clinical results from our multicenter trial of cryotherapy for breast fibroadenomas have been previously reported (2), and only unique patient features (ie, multiple probes, thermocouples, histologic evaluation) and imaging findings are reported here. The imaging details and characteristics of our patient population are reported in this article to highlight cryobiology principles of selected freeze protocols, available histologic results, longer US imaging outcomes, and potential racial implications. We found the procedure to be easily monitored with US, virtually painless, and highly amenable to a breast clinic or outpatient radiology setting, and it can be performed with only local anesthesia. US also provided reliable follow-up over time, corroborating encouraging clinical outcomes of resolved mass effect and excellent skin cosmesis. Other than transient hypopigmentation at the insertion site, African American patients responded to cryotherapy as well as white patients and showed no evidence of increased keloid formation (17).

Despite common racial trends regarding fibroadenomas and keloids (4–7,18), the most impressive outcome was in a white adolescent who showed nearly complete palpable resolution of seven fibroadenomas treated over an 18-month period (five sessions). She also experienced marked improvement in psychological status and social affect as a result of avoiding contemplated bilateral mastectomies, since she had formed keloids at each of her four resections sites prior to enrolling in this study. Her unusual case (ie, white) still suggests potential connections between benign conditions of altered growth factors. Further work is needed on the etiology of increased fibroadenoma incidence (4–7), keloids (18), and leiomyomata (19) in African-American women, as well as on the potential immune connection of developing fibroadenomas in patients undergoing cyclosporine therapy after transplantation surgery (20). Cryotherapy thus appears

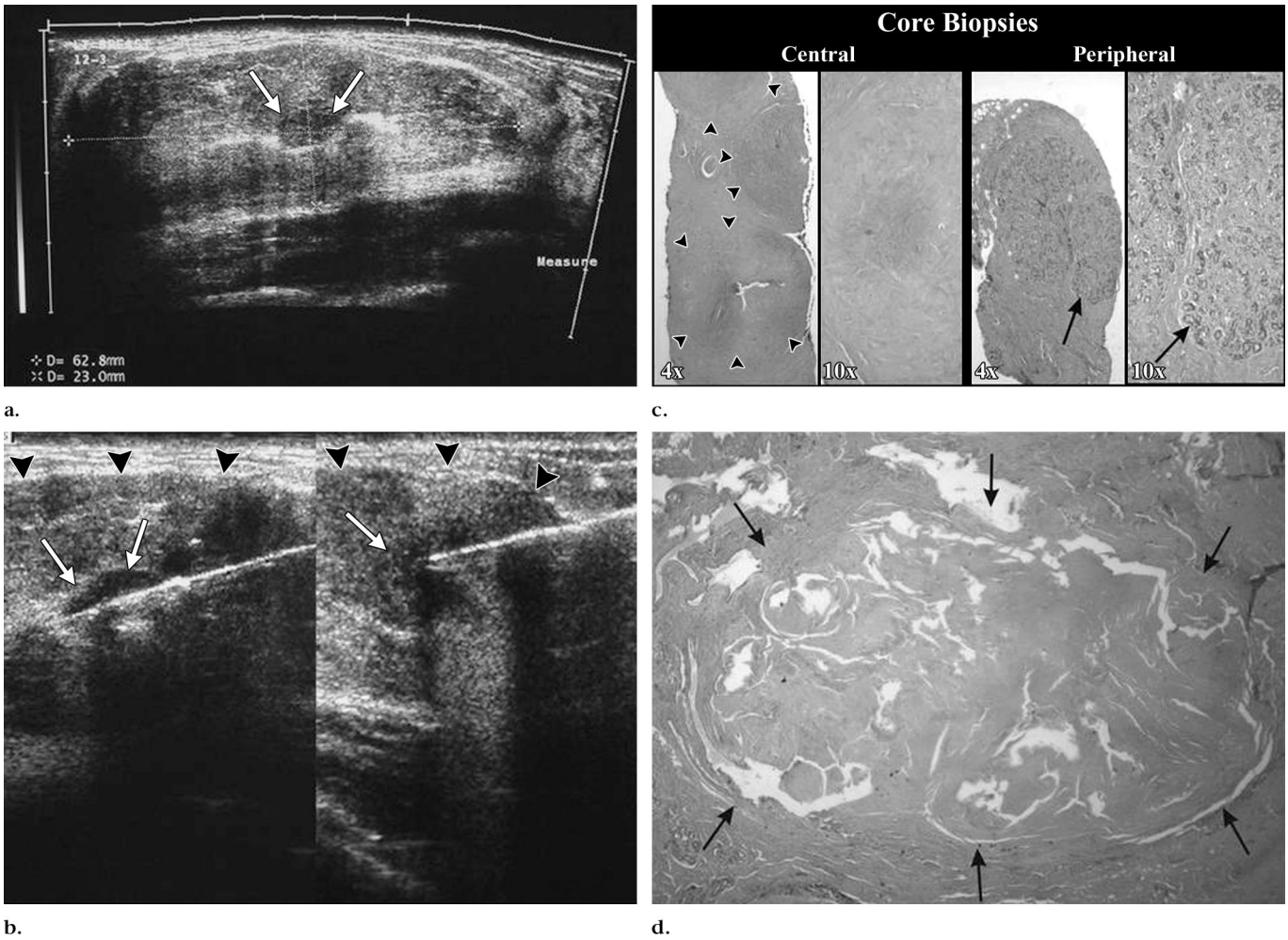


Figure 5. **(a)** US image shows potentially aberrant healing reaction (calipers, 6.3 × 2.3 cm) 6 months after cryotherapy, consisting of a well-circumscribed hypoechoic area surrounding the atrophied fibroadenoma (arrows). **(b)** US image of core biopsy specimens of the central (left) and peripheral (right) components of the healing reaction. Hypoechoic margin of the masslike healing reaction (arrowheads) and shrunken underlying fibroadenoma (arrows) are seen. **(c)** Images of central and peripheral biopsy specimens from **b** at two magnifications. Central biopsy specimens confirm residual whirled architectural pattern of fibroadenoma (×4; arrowheads) replaced by a paucicellular hyaline background (at ×10). Peripheral biopsy specimens show normal parenchyma with glandular epithelium (arrows). (Hematoxlyin-eosin stain). **(d)** Low-magnification whole-specimen view of resected fibroadenoma treatment site (arrows) in the woman who elected to have residual palpable mass effect removed despite US volume reduction (70%). Note acellular central hyaline background without evidence of residual viable fibroadenoma tissue. (Hematoxlyin-eosin stain; original magnification, ×2).

encouraging for special patient groups with multiple and/or growing fibroadenomas.

Important freeze protocol details and equipment differences were not covered in our initial article (2) but can now be better compared (14). Pfleiderer et al (14) documented mean iceball diameters over time by using a 3-mm probe (CryoHit; Galil, Yokneam, Israel) in 16 breast cancers. A notable difference is the speed in achieving a 2.0-cm iceball during the first freeze, which took less than 4 minutes in our series but took approximately 6 minutes with the 3-mm probe in the study by Pfleiderer et al. While the final iceball size of 2.7 cm (after two 7-minute freezes) in that study was similar to our final diameter of approximately 2.9 cm in protocol 3, ours was achieved by using only 4-minute freeze cycles at 100% flow rate. Pfleiderer's group did not record tissue temperatures; they reported only on temperatures from within the probe. In our series, we have shown that thoroughly cytotoxic temperatures (<−40°C) (15–17) occur approximately 5 mm behind the visible second freeze margin during the second freeze and were achieved with faster, more lethal freeze rates. The air-gap–insulated probes used in this study have been replaced by vacuum-insulated trocar-tipped 2.7-mm cryoprobes, eliminating the need for skin protection at the insertion site.

Our clinical success (73% tumor volume reduction and reduction of palpability to acceptable levels in 89% of cases) may relate to a combination of our technique, probe characteristics, short-axis fibroadenoma diameters, and freeze protocols. The protocols used maximal fibroadenoma measurements, yet our technique placed the long axis of the fibroadenoma along the probe shaft to take advantage of the probe's approximately doubled freeze length compared with its width or depth. Therefore, the short-axis diameters of the fibroadenoma are more important for precise tumor targeting than is the overall average diameter. Over-freezing beyond

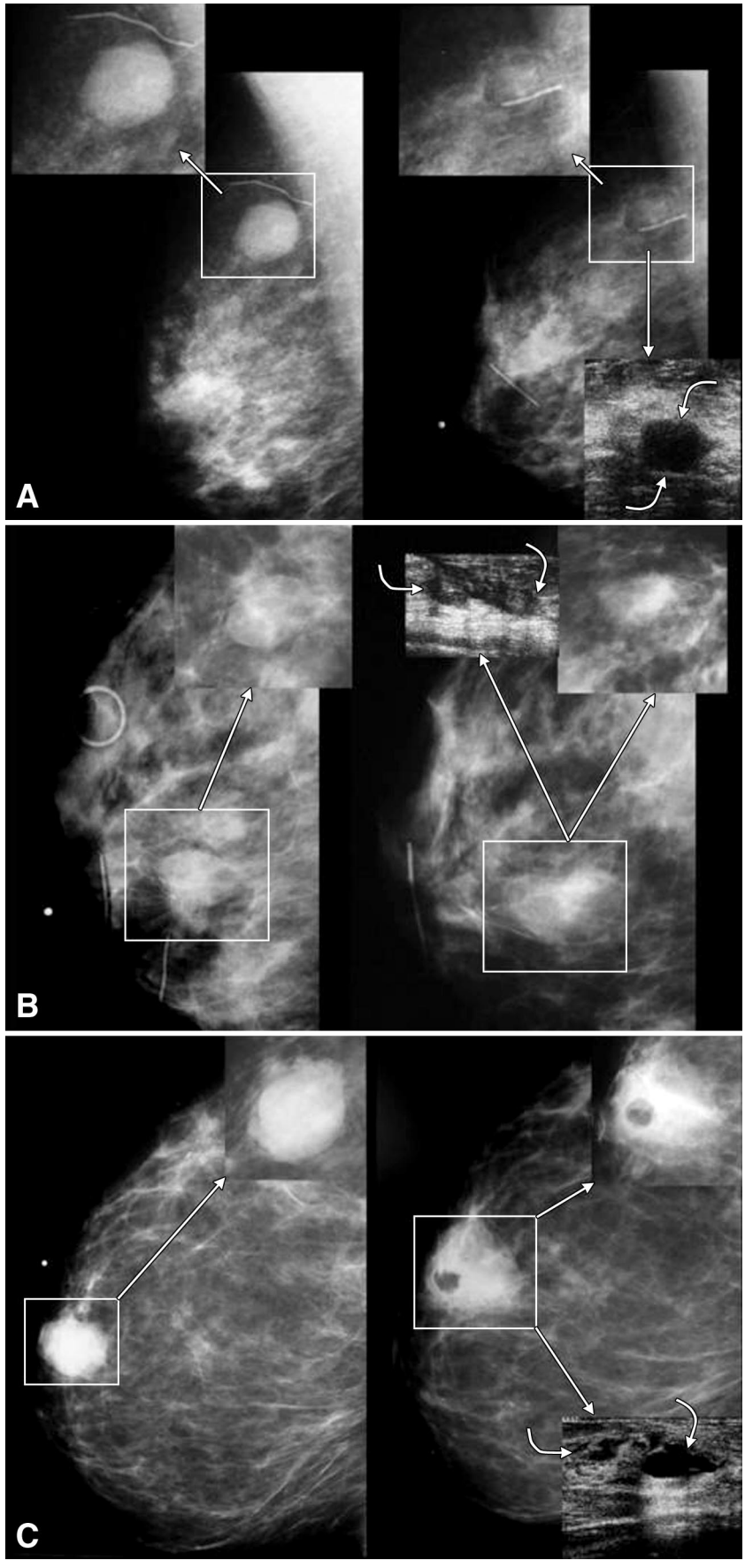


Figure 6. Mammograms with US correlates show changes with cryotherapy at 1 year. *A*, Mediolateral oblique mammograms of 2.5-cm left axillary tail mass before cryotherapy (left) show minimal mass effect after cryotherapy (right); top inset on each image is a magnified view. However, the US image (bottom inset, postcryotherapy image) shows a residual small mass effect (curved arrows). *B*, True lateral mammograms of a distinct central mass within dense breast parenchyma before cryotherapy (left) also shows minimal mass effect after cryotherapy (right), which is better seen in compression views (right inset on each image). The follow-up US image (left inset, postcryotherapy image) only shows ill-defined parenchymal changes (curved arrows). *C*, True lateral mammograms of a 2.8-cm periareolar mass in a fatty breast before cryotherapy (left) show a slightly greater surrounding density after cryotherapy (right), with a central oil cyst; top inset on each image is a magnified view. US image (bottom inset, postcryotherapy image) shows cystic component (curved arrow on right) and adjacent ill-defined parenchymal changes (curved arrow on left).

the limits of the tumor in the longitudinal axis (eg, smaller tumors) and under-freezing in the short axis (eg, larger tumors) may be easily remedied by using newer vacuum-insulated cryoprobes. These will also be modified to have shorter longitudinal freeze dimensions for more spheroid ice that better matches tumor shapes. Probe selection options will allow greater treatment flexibility while lessening the burdens of precise central probe placement in a firm tumor lying within loose breast fat (ie, mobile and operator-dependent). Rapidly advancing cryotechnology will also be crucial for cancer applications that have great potential for breast conservation yet require thorough understanding of cryobiology principles (14).

Many of our patients who had maximal tumor diameters of less than 2 cm ($n = 15$) were adolescents and other nulliparous females, for whom future lactation is a concern. We thus modified our freeze protocol after this trial to reduce excessive necrosis of normal tissue while maintaining aggressive freeze parameters. Rapid dual freezes could minimize the role of the "maintenance" portion of each freeze (16,17). This dual-freeze technique is similar to current prostate freezing protocols that use tightly controlled thermocouple monitoring (15), which has recently progressed to automated control of multiple cryoprobes by way of adjacent thermocouple readings (AutoFreeze, Endocare). Yet the longer a freeze is held near the maximum iceball capac-

ity of each probe, the colder the isotherm becomes at the ice margin (−29°, −38°, −45°C for protocols 2, 3, and 4, respectively).

While we are confident that standardized freeze protocols can work well for less-experienced physicians, we currently emphasize close monitoring with US for all mass sizes. For masses less than 2 cm in short-axis diameter, we rapidly push the ice margin 3–5 mm beyond the fibroadenoma margins at 100% duty cycle, thaw for at least 6 minutes, then rapidly refreeze to even greater ice size. For larger masses that approach the maximal freeze capacity of the cryoprobe (ie, ice expansion slows to "maintenance" rates of approximately 0.1 cm/min), longer freeze times are needed to achieve the expansion of the lethal isotherm, as seen in the later portion of the freeze curves. Larger freezes approaching 3 cm may need to be held for up to 10 minutes each, with an interposed thaw for more than 6 minutes. Alternatively, we also now use a bracketing approach for masses that are 3–4 cm, whereby we place two probes approximately 1.5–2.0 cm apart to allow rapid freezing and to thoroughly cover tumor margins. We recognize that these modifications require greater operator dependence. However, ice monitoring after probe placement is easily seen by using high-frequency (ie, high spatial resolution) linear-array breast US transducers, similar to the exquisite monitoring of hepatic cryotherapy by using intraoperative US (21).

The limited confirmatory tissue from this series corroborates pathologic findings of cryotherapy in other organ systems. Minimal scarring from cryotherapy makes it widely used for many dermatologic conditions (22). The preservation of collagenous architecture in a fibrous target (23) helps explain why postcryotherapy prostates maintain similar shape and size, while biopsy specimens show only a hyaline-replaced matrix (15). Similarly, the lack of perforation and/or destruction of the cartilaginous rings of the bronchial tree by using cryotherapy led some to suggest its superiority over heat-based ablations for endobronchial neoplasms (24). The excellent cosmetic outcome (ie, 80% palpable resolution and minimal skin-puncture site) for patients in our series suggests minimal scarring, with similar architectural preservation of the shrunken fibroadenoma collagen matrix. The lack of satisfactory palpable shrinkage in the one patient who elected to undergo resection may relate in part to the relatively fibrous nature of the pretreatment biopsy specimens (ie, similar to the more fibrous architecture of prostates showing minimal shrinkage). Further work is needed to assess whether hypocellularity in pretreatment biopsy specimens may serve as a prognostic indicator for satisfactory cryotherapy response (ie, is the fibroadenoma more on the "fibro" or the "adenoma" end of the spectrum?).

US also served as a surrogate for histologic response at follow-up. Early increased echogenicity of ablated tissue beyond the fibroadenoma and the early hypervascular rim mostly likely relates to acute edema and an inflammatory infiltrate at those sites (22). The increasingly hypoechoic appearance over time likely represents tissue involution and organization that is similar to a healing hematoma. One patient did have a small cystic area develop within the fragmentation of the primary fibroadenoma by 6 months. This "autofragmentation" phenomenon corresponded to virtual resolution of the palpable area in most patients. The central areas of the fibroadenoma scar on US images also appeared to closely correspond to pathologic measurements of the hyaline replacement in the shrunken collagenous architecture of the former fibroadenoma. While the mammographic data are limited, they suggest a similar overall healing course, with decreased mass effect and no evidence of dystrophic calcifications.

The potential aberrant tissue reactions surrounding the involuted fibroadenoma in three (11%) of 27 patients are difficult to understand in the face of histologic results from biopsy and resection specimens that showed normal surrounding breast parenchyma. We can only postulate an exacerbated healing reaction that may have a complex immunologic, genetic, and/or hormonal basis. Cryoablation zones have a surrounding hypervascular rim, which has been shown to create apoptosis in cells near the periphery that do not die immediately (22). Cells surviving those apoptotic mechanisms may be prone to hyperstimulated growth, whether that is from hormonal, vascular, or other stimuli. The idiosyncratic tissue reactions seen in our patients most likely incorporate several facets of these complex interactions, suggesting both caution and future treatment possibilities for any malignancy. Specifically, cryotherapy for breast cancer requires detailed knowledge of US-driven freezing protocols to avoid under-treatment of tumors larger than 1.5 cm (14). Likewise, the hypervascular rim suggests a potential for enhanced chemotherapy delivery or greater sensitization to radiation. Regardless of the type of image-guided breast cancer treatment, clear definition of tumor margins in relation to treatment margins will be crucial (25). This may require further developments in US to provide clear tissue differentiation (26) and monitor treatment outcomes rather than rely on the costly and limited access of magnetic resonance imaging (27).

Limitations of the current study involve the rapidly developing cryoablation technology and associated technique modifications. During the course of this study, an important cryoablation technology advancement included the vacuum jacket of the cryoprobes, which thereby removed the need for an insertion trocar or associated continuous fluid dripping for skin protection. In addition, it was noted that saline injection was needed only for skin overlying a fibroadenoma, since the underlying pectoralis muscle could be protected by simply elevating the whole probe with gentle to-and-fro movement. The thermocouple monitoring performed for this study was done primarily for definition of freezing protocols to help automate the equipment for physician offices or clinics. However, practicing radiologists will recognize the ease of use in simply monitoring the echogenic iceball as its rim extends 0.5 mm beyond the fibroadenoma margin. The operator dependence of placing the probe within the center of a lesion may be a limitation for less-skilled imagers but also emphasizes the important role of radiologists for this procedure. As cryoablation technology gets applied to breast cancer in the future, the need for thermometry to ensure cytotoxic temperatures beyond well-visualized tumor margins becomes more critical, similar to prostate cryotherapy, in which thorough treatment of even aggressive tumors has been validated (14).

In summary, scarring and cosmesis are not trivial concerns for patients undergoing breast surgery, especially for women with multiple tumors, history of keloid formation, or prior excisions. Cryotherapy of breast fibroadenomas causes minimal discomfort and can provide improved cosmesis with which patients are very satisfied. In addition, costs for treating benign tumors may be reduced by preventing open resection, as well as by treating tumors in an outpatient clinic setting rather than in an ambulatory surgery setting.

Acknowledgment: The authors thank all health care workers associated with the development of breast cryotherapy, specifically Dianna Hatch, BS, ARDMS, for all US coordination and the staff of the Walt Comprehensive Breast Center.

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Chapter 18
Ultrasonography Guided Nonsurgical Cryoablation for Small Breast Cancer

Eisuke Fukuma

18.1 Background

Cryotherapy for the treatment of human disease has a long history dating back to the reported treatment of cancer by James Arnott in 1845 [1] and cryotherapy has been applied for various kinds of skin disease in the late nineteenth century and early twentieth century. Indication of cryotherapy was extended to other organs, including lung [2], kidney [3], and liver [4] amongst others [5] after the late twentieth century. The Japan Society for Low Temperature Medicine was established in 1974.

Cryotherapy for breast disease is divided into several treatments. One of those is nonsurgical cryoablation for malignant [6, 7] and benign breast disease [8]. Another treatment is palliative cryotherapy for intractable bleeding from ulcerative breast cancer and a third treatment is cryoablation-assisted lumpectomy (CAL) [9].

Nonsurgical cryoablation for small breast cancer is mentioned in this chapter.

18.2 Theory of Cryoablation

Two mechanisms of the tumour-killing effect of cryoablation are known as rapid cooling and slow cooling (Fig. 18.1a). Rapid cooling near the probe, used for cryoablation, causes intercellular freezing, followed by mechanical destruction of the cell membrane with ice crystals. Slow cooling happens several mm inside the ice ball from its edge. Destruction of the cancer cell is explained with mechanical stress from the ice crystals, chemical stress (increasing electrolyte concentration),

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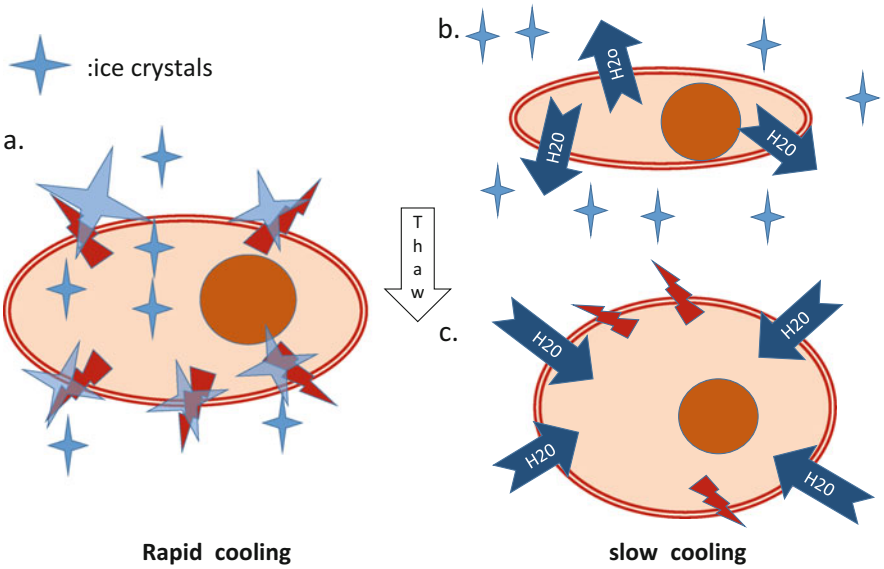

Fig. 18.1 Mechanism to destroy tumour cell with cryotherapy. (**a**) Rapid cooling (intracellular freezing): ice crystals are formed inside and outside tumour cells destroying the cell membrane directly (mechanical stress). (**b**, **c**) Slow cooling (extracellular freezing). (**b**) Flow of intracellular fluid to extracellular space causes shrinkage of the cells. (**c**) During time of thaw, influx of H2O from extracellular space to inside of the cell results in overexpansion of the cell, followed by mechanical stress and destruction of cell membrane. Outflow and influx of H2O in the cell causes rapid change of osmotic pressure and concentration of electrolytes (osmotic and chemical stress)

and osmotic stress (high osmotic pressure inside the cell caused by shrinkage of cells; Fig. 18.1b). Death of tumour cells is expected at less than −40 °C and this death varies according to the kind of cells Total death of tumour and normal cells is expected 5–8 mm away from the edge of the ice ball.

18.3 Equipment for Cryoablation of Breast Cancer

Freezing of breast cancers is achieved with insertion of the probe into the mass. The probe is expected to reach to −120–170 °C. Achieved lowest temperature varies according to the machines for freezing. Machines for cryotherapy for breast disease are divided into two different principles of freezing: argon-gas–based technology and liquid-nitrogen–based technology. CryoHit (Galil Medical C.C) and Visica I (Sanarus C.C, Fig. 18.2a not commercially available at present) are based on principle of the Joule and Thomson phenomenon with argon and helium gas. IceSense3 (IceCure C.C Fig. 18.2b) and Visica II (Sanarus C.C) depend on the freezing power of liquid nitrogen.

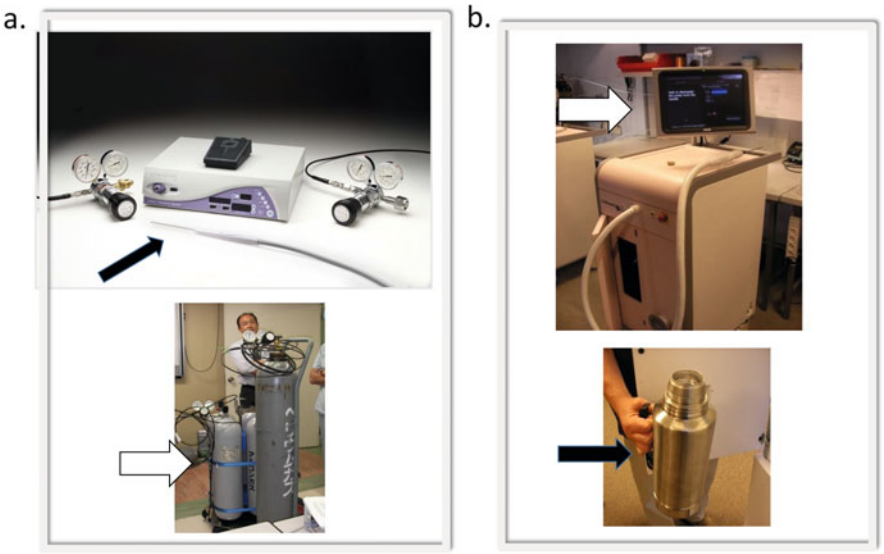

Fig. 18.2 Machine used for cryoablation for breast disease. (**a**) Visica I (Sanarus C.C) is based on Joule Thomson principle with high pressure argon and helium gas). Probe for insertion (*black arrow*). High pressure tanks are prepared for high pressure argon and helium gases. (**b**) IceSense3 (IceCure C.C) is based on cooling with liquid nitrogen. White arrow shows touch panel console on the top of the main body to control time of freezing, thaw, and warming. Also amount of flow volume to the probe is monitored with the console. Lower part of the main body store 2 l volume container of liquid nitrogen (*black arrow*)

IceSense3 has been used for nonsurgical cryoablation for small breast cancer at our institution since 2013. The main body of IceSense3 holds the container of two liters of liquid nitrogen, the console to regulate the inflow of liquid nitrogen into the probe and outflow of the gas nitrogen, and the conduit of liquid nitrogen from the main body to the probe. The probe is disposable and attached to the conduit in screwed attaching fashion. The diameter of the probe is 3.4 mm with a sharp tip and the active freezing zone is 20 mm and 40 mm of small and large probes each; the active freezing zone of the probe creates −170 °C at the lowest temperature (Fig. 18.3).

18.4 Indication of Nonsurgical Cryoablation

The size of the ice ball formed with IceSense3 reaches from 35 mm to more than 45 mm transversely to the probe and 40–50 mm longitudinally. The size of the cell death effect is expected within 5–8 mm away from the edge of ice ball (Fig. 18.4). If formed, the transverse size of the ice ball is 40 mm; within 24 mm in transverse size is expected to achieve cell destruction. Longitudinally, the size of ice ball reaches to

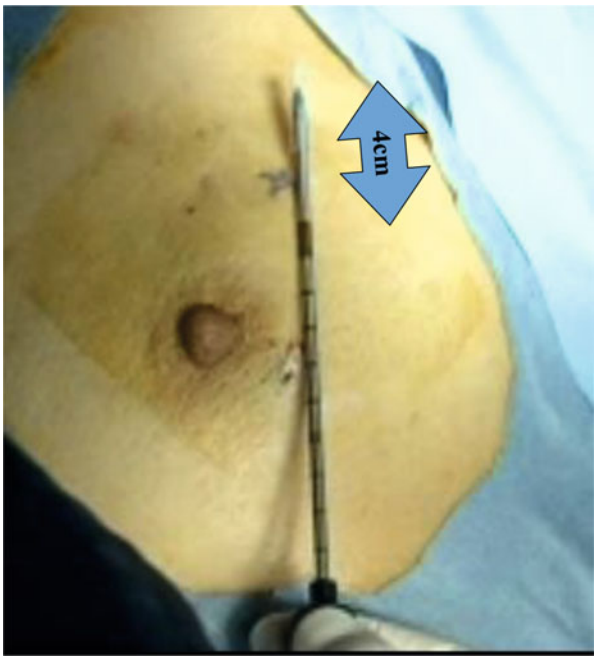

Fig. 18.3 Probe of IceSense 3 system. Probe of IceSense 3 system is 3.4 mm in diameter and active zone of freezing is 4 cm long (*white arrow*)

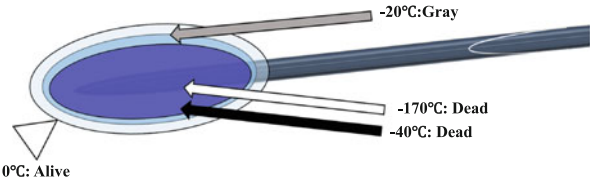

Fig. 18.4 Temperature gradient from the probe, which reaches to −170 °C. From the probe (*white arrow*) to −40 °C zone (*black arrow*) death of the tumour is expected. Death of the tumour cell from −40 to −20°C zone is gray and tumour-killing effect depends on type of cancer (*gray arrow*). Cancer cell is alive around the ice ball edge (0°C: *white arrow head*)

more than 40 mm when a large probe is used. The probe should be inserted along the longest diameter of the lesion and the direction of the longest diameter of the lesions is achieved along the radial direction from the nipple in most occasions. Lesion size should be measured with mammography, ultrasonography, and breast MRI and size of the lesions should be less than 10 mm (Figs. 18.5 and 18.6) because of the limited cell-destroying zone within the formed ice ball and the safety margin, 3–5 mm, from the targeted lesion to achieve local control of the cancer.

At present, biology of the cancer is important to choose the candidate for nonsurgical cryoablation and other than Luminal A-like lesions should be excluded as candidates. Moreover, a negative of sentinel node metastasis and distant metastasis are crucial for indication of nonsurgical cryoablation.

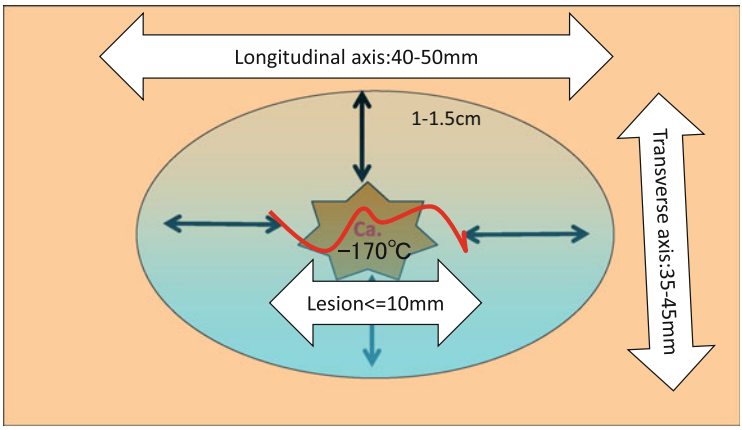

Fig. 18.5 Indication of nonsurgical cryoablation for small breast cancer. Size of formed ice ball with IceSense3 is 35–45 mm in transverse axis of the probe and 40–50 mm in longitudinal axis. Transversely 40-mm sized ice ball expects 24-mm sized area to destroy cancer lesion. The lesion, including mass and DCIS, have to be less than 10 mm

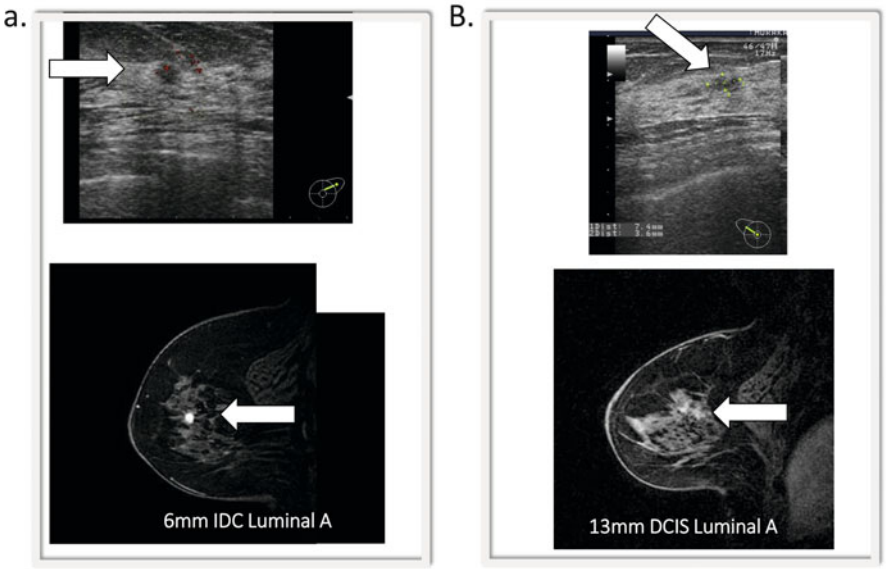

Fig. 18.6 Candidates are selected with breast imaging. (**a**) Candidate. Both ultrasonography and breast MRI showed localised lesion less than 10 mm (*white arrows*). (**b**) Not candidate. Although the lesion was less than 10 mm with ultrasonography (*white arrow*), breast MRI disclosed 13 mm long lesion

Based on inclusion criteria and longstanding experience of nonsurgical cryoablation, the number of nonsurgical cryoablations is increasing in a number of patients having local control, mastectomy, breast conservative surgery, and nonsurgical cryoablation for breast cancer (Fig. 18.7).

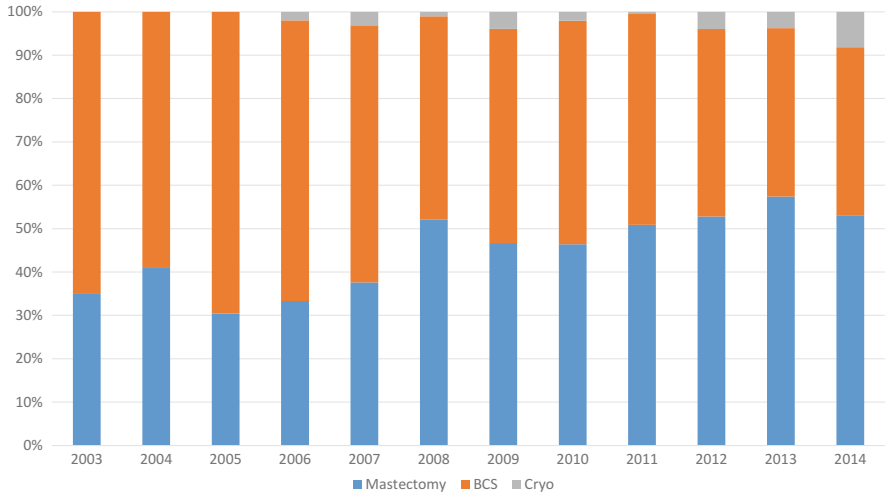

Fig. 18.7 Serial change of breast surgery at Kameda Medical Center. Nonsurgical cryoablation for breast cancer among breast surgeries has been increasing in numbers since 2006 and 8.2 % of surgery is done with nonsurgical cryoablation in 2014

18.5 Evaluation Before the Procedure and Follow-Up After the Procedure

Before the decision of indication, physical examination, ultrasonography, mammography, and/or breast MRI are performed to know the lesion size. A PET scan is mandatory, according to the staging of breast cancer. Also vacuum assisted biopsy (VAB) or core needle biopsy (CNB) has to be performed to learn the pathology and subtype of the breast cancer. VAB is recommended because of the larger amount of the specimen. Sentinel node biopsy (SNB) is needed to know the nodal state of the patient with invasive breast cancer, which is disclosed by VAB or CNB. SNB is able to be eliminated for the patient with DCIS, the lesion of which is nearly or totally excised with VAB.

The first step for successful cryoablation is a breast MRI to learn the proper targeting of the lesion after 1 or 1.5 months after the cryoablation. If calcification of the lesion is identified with mammography before cryoablation, mammography is added to learn the proper targeting at the first postprocedural breast imaging. And then 6 and 12 months after the procedure, a breast MRI and other modalities of breast imaging are performed to learn in-breast tumour recurrence (IBTR).

After identifying the proper targeting of the lesion, whole breast irradiation and hormonal therapy are scheduled.

18.6 Practice of Nonsurgical Cryoablation

Nonsurgical cryoablation can be performed under local anesthesia and with day surgery. Setting up of the procedure is simple: 20 cc of 1% lidocaine with epinephrine and 23 G needle, scalpel, and normal saline to prevent thermal injury of the skin from ice ball (Fig. 18.8a, b). Four liters of liquid nitrogen are needed for 20-min freezing time.

The patient lies down on the back and an intravenous line inserted. In most patients, the site of insertion of the probe is the periareolar region. In some patients with the cancer in the lower part of the breast, a skin incision is added along the inframammary fold. The skin incision should be selected to achieve penetration of the probe along the longest caliber of the lesion (Fig. 18.9).

Before adding the skin incision, local anesthesia is injected into the incised site, needle tract, subcutaneous area, and behind the major pectral fascia. When the

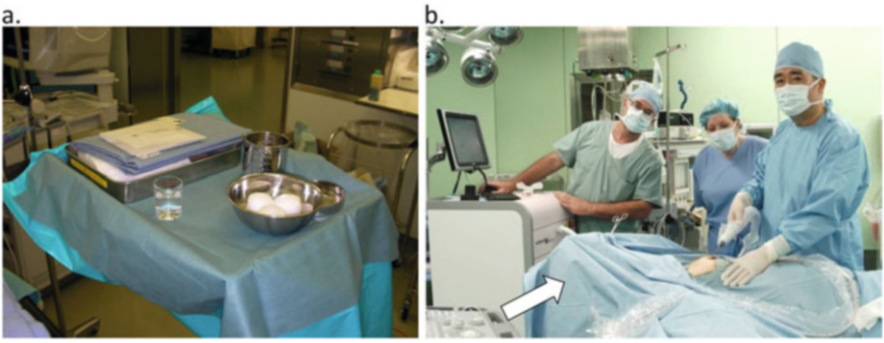

Fig. 18.8 Setup for nonsurgical cryoablation. (**a**) Preparation. 20 cc of 1 % lidocaine with epinephrine. 23G needle. Scalpel. Normal saline. Dressing. Gauze. Material and instruments for one stitch closure. Pean. (**b**) Staff and positioning. One surgeon, medical engineer, and circulating nurse are enough for the procedures. Head of the patient is indicated with *white arrow*

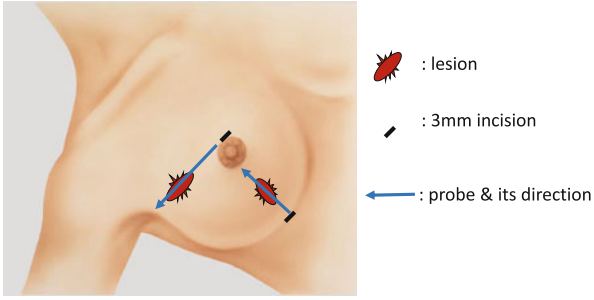

Fig. 18.9 Selection of incision site. Site of incision is selected according to relative location of the lesion and longitudinal axis direction of the lesion

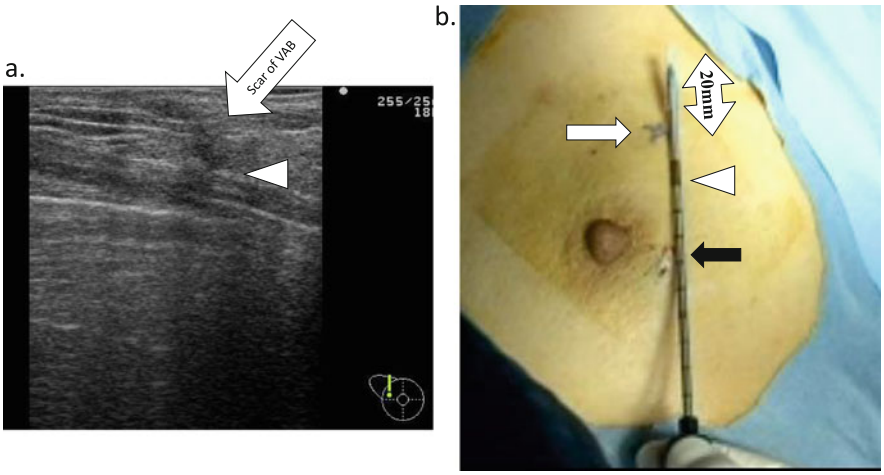

Fig. 18.10 Evaluation of the lesion and the breast before adding incision. (**a**) Evaluation with ultrasonography. The lesion is barely identified with ultrasonography (*white arrow*) in thin thickness breast. Injection of local anesthesia should be given in the space below the pectral major fascia (*white arrow head*). After penetration of the lesion with the probe, local anesthesia is administered under the skin. (**b**) Proper incisional site. Location of the skin surface mark above the lesion (*white arrow*) is 20 mm away from tip of the probe. Incision site (*black arrow*) should be more than 10 mm away from active freezing zone (*white arrow head*)

lesion is hardly identified because of a small lesion or postbiopsy state, injection of that should be after penetration of the lesion with the probe (Fig. 18.10a).

Through a 3 mm long skin incision, a large probe is inserted along the longest lesion site.

The distance from the tip of the probe to the mid portion of the lesion should be around 20 mm because the lowest temperature is expected at that point (Fig. 18.10b). In most cases, the probe penetrates the centre of the lesion. When the size of the breast with the lesion is not thick, the probe is inserted into the relatively dorsal part of the lesion. In the case of mucinous cancer, penetration of the lesion is avoided as much as possible.

IceSense3 has a programmed and manual mode of freezing, thaw, and warming. One treatment session with IceSense3 consists of first freezing, thaw, second freezing, and warming (double-freezing method). The manual mode of the program is frequently used because adjusting the size of the ice ball is easier than the programmed mode. Although the longitudinal axis along the large probe becomes larger than 40 mm, the size of the ice ball along the transverse axis should be controlled by measuring its size with ultrasonography (Fig. 18.11). The transverse axis diameter is decided according to the size of the lesion, breast thickness, and location of the probe inside the lesion.

After the cryoablation finished, the probe is extracted. The incision is closed with absorbable suture in one stitch. The incision is covered with a few sheets of

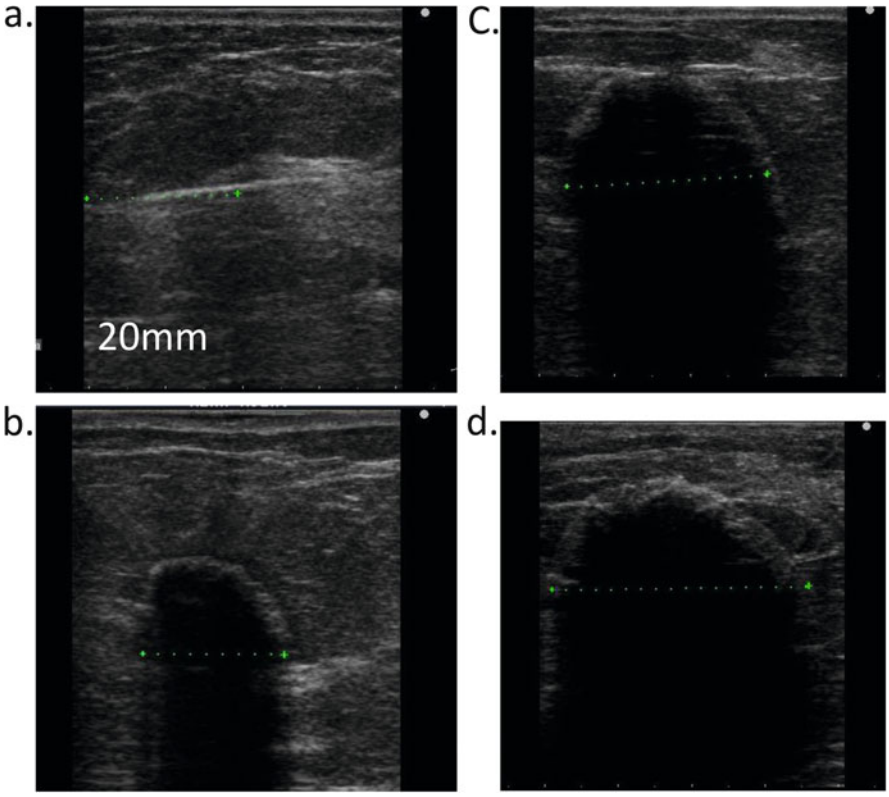

Fig. 18.11 Observing growing ice ball with ultrasonography. (**a**) Distance from tip of the probe to the lesion is 20 mm along longitudinal axis of the probe. (**b**–**d**) Measurement of growing ice ball along transverse axis of the probe is easy with ultrasonography. The ablated zone can be controlled well with these procedures

gauze but do not compress too much to avoid pressure necrosis. The total time of the whole session takes 60–70 min, but the actual freezing time is 12–22 min (double-freezing method) and 6–10 min thaw time.

One day after cryoablation, the patient visits as an outpatient to remove the dressing and check the treated breast.

18.7 Technique of to Achieve Successful Cryoablation Anywhere and Any Size of the Breast

Breast size among Asian women is smaller than that of Caucasian women and thickness of the breasts is different according to location of the lesions. The size of the ice ball is expected to be larger than 35 mm to destroy the cancer cells of 10-mm

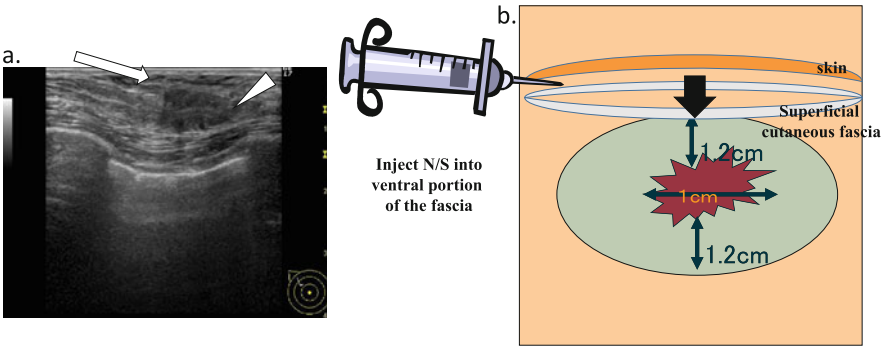

Fig. 18.12 Protecting the skin is achieved by injecting saline in the space between the skin and the superficial cutaneous fascia. (**a**) Image with ultrasonography. Although the lesion is closed, the injection made the gap between the skin and the superficial subcutaneous fascia. This lesion is a candidate because the gap could be expanded with injecting saline. (**b**) The space between the skin and the subcutaneous fascia can be expanded by injecting saline. The ice ball engulfs the fascia

size lesions even though thickness of the breast, where the lesion is located, is less than 15 mm. If cryoablation is applied for all candidates who satisfy the inclusion criteria, a cautious approach is demanded to avoid thermal injury of the skin and the chest wall, especially among patients with thin breasts. During the freezing procedure, the probe is lifted up and shaken to prevent thermal injury to the chest wall. Injection of normal saline to the space between the skin and the subcutaneous fascia is carried out to avoid thermal injury to the skin (Fig. 18.12a, b). The gap between the skin and the fascia is expanded enough to prevent thermal injury by injecting saline. Saline should be injected accurately into the adjacent area under the skin with an ultrasonography-guided procedure.

Destroying the cancer cells can be achieved even though the lesion is adjacent to the subcutaneous fascia with injecting saline when the distance from the fascia to the edge of ice ball beyond the fascia (Fig. 18.13a–d). The volume of saline into the gap is unlimited and the several patients who received more than 350 cc of saline injection to avoid thermal injury to the skin were experienced.

18.8 Serial Change of Breast Imaging After Nonsurgical Cryoablation

It is important to know the serial change of breast imaging after cryoablation to distinguish inflammatory change after cryoablation from IBTR. A breast MRI one or 1.5 months after cryoablation, aimed to discover the proper targeting of cryoablation, shows granulation formed at the ablated area (Fig. 18.14a, b) and peripheral enhancement around the granulation is observed. Peripheral

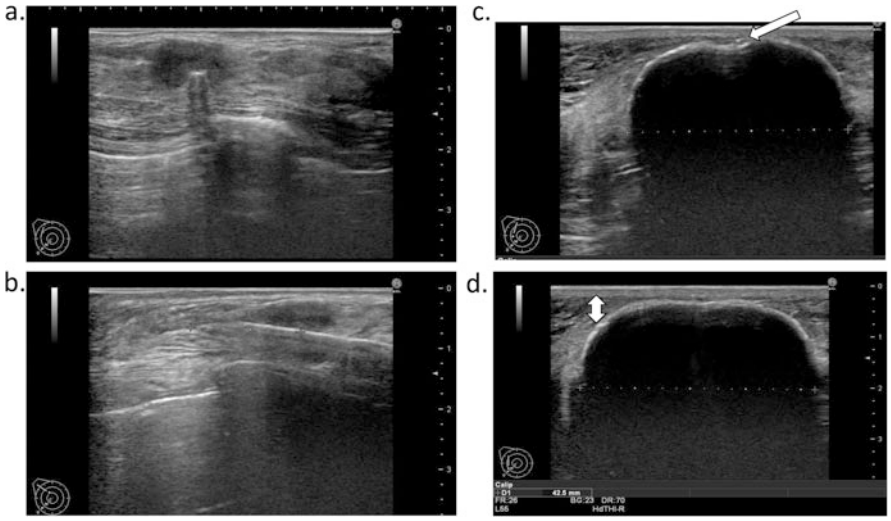

Fig. 18.13 Finding a way to perform cryoablation in thin thickness breasts. (**a**) Ultrasonography with transverse axis of the probe before freezing. The probe was inserted into the dorsal part of the lesion because of assurance of cancer extirpation of dorsal part. (**b**) Ultrasonography with longitudinal axis of the probe before freezing. The probe was inserted into the dorsal part of the lesion because of assurance of cancer extirpation of dorsal part. (**c**) Ultrasonography with transverse axis of the probe after freezing. Growing ice ball adjacent to the skin was accurately observed. 23G needle, injecting saline, was identified (*white arrow*). (**d**) Ultrasonography with transverse axis of the probe after freezing. End of second freezing. Size of the ice ball along transverse axis was 42.5 mm. Gap between the skin and the fascia is more than 5 mm

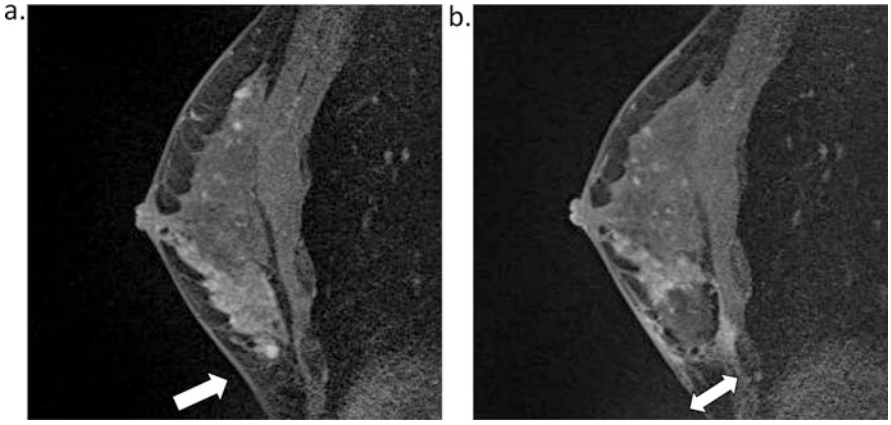

Fig. 18.14 Breast MRI 1–1.5 months after cryoablation to know accurate targeting of the lesion. (**a**) The lesion before cryoablation (*white arrow*). (**b**) After cryoablation, targeting the lesion was performed well. Ablated area from the skin and part of the muscle was observed. No thermal injury of the skin is observed

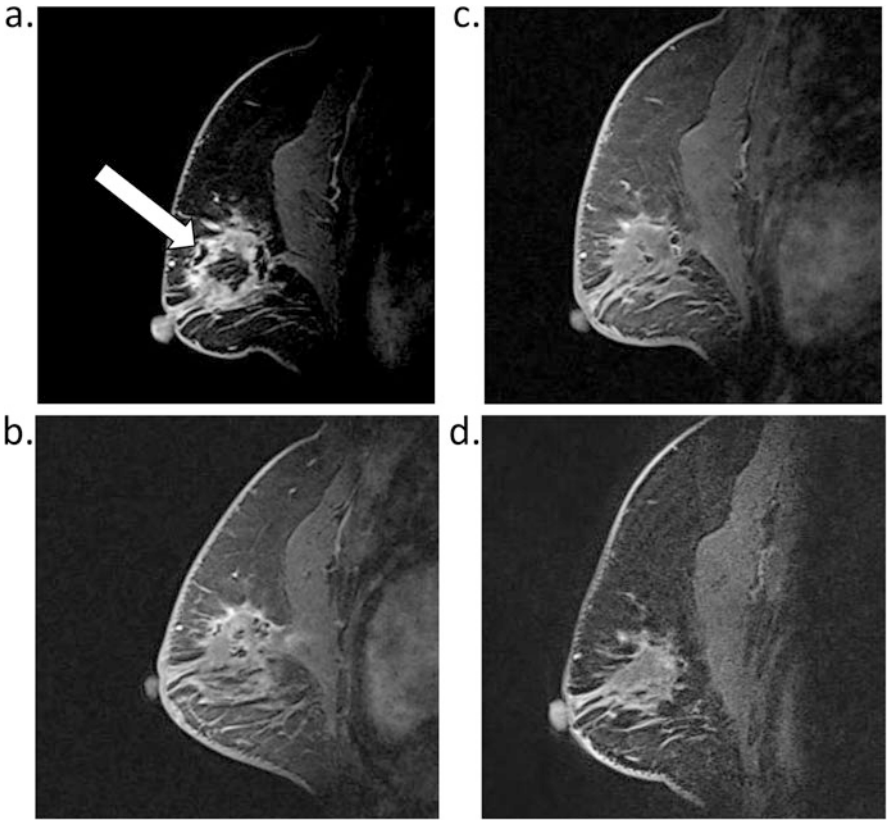

Fig. 18.15 Serial changes of breast MRI after cryoablation. (**a**) One month after: peripheral enhancement around the granulation was noted (*white arrow*). (**b**) Six months after: peripheral enhancement subsided. (**c**) Eleven months after. (**d**) Thirty-three months after: peripheral enhancement was diminished. Granulation was smaller than before

enhancement is subsided serially after 6 months and then it is speculated to be able to diagnose IBTR (Fig. 18.15a–d).

Although the density of the ablated area of the breast is high after cryoablation, calcification remaining in the breast after cryoablation is easily identified with mammography. Mass lesion or distortion is hardly recognised with mammography (Fig. 18.16a–c).

Granulation formed after cryoablation, identified with ultrasonography, also gradually grows smaller in size (Fig. 18.17a–d). Imaging inside the granulation varies.

One IBTR after nonsurgical cryoablation is experienced. IBTR was developed 5 years after cryoablation for T1a Luminal A invasive breast cancer. Although it was recognised with breast MRI and mammography, ultrasonography failed to find the lesion. MR-guided VAB disclosed DCIS in the lesion (Fig. 18.18).

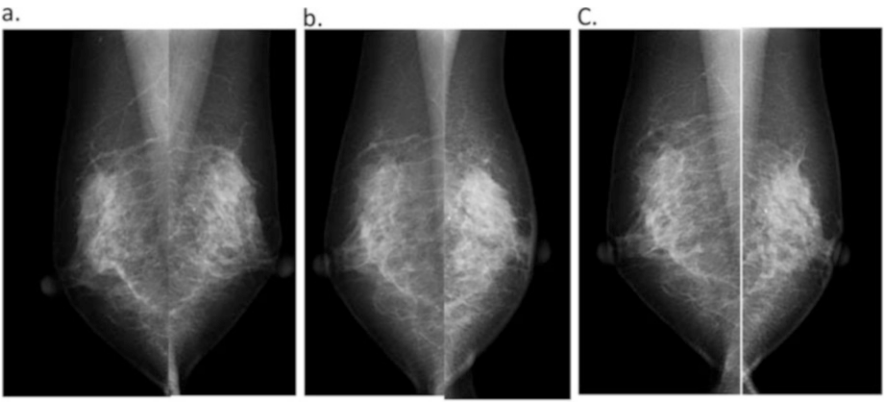

Fig. 18.16 Serial changes of mammography after cryoablation. (**a**) Preoperative mammography: cancer was in upper region of left breast. (**b**) Eleven months after cryoablation: High density was noted at the ablated area. (**c**) Thirty-three months after: area of high density was smaller

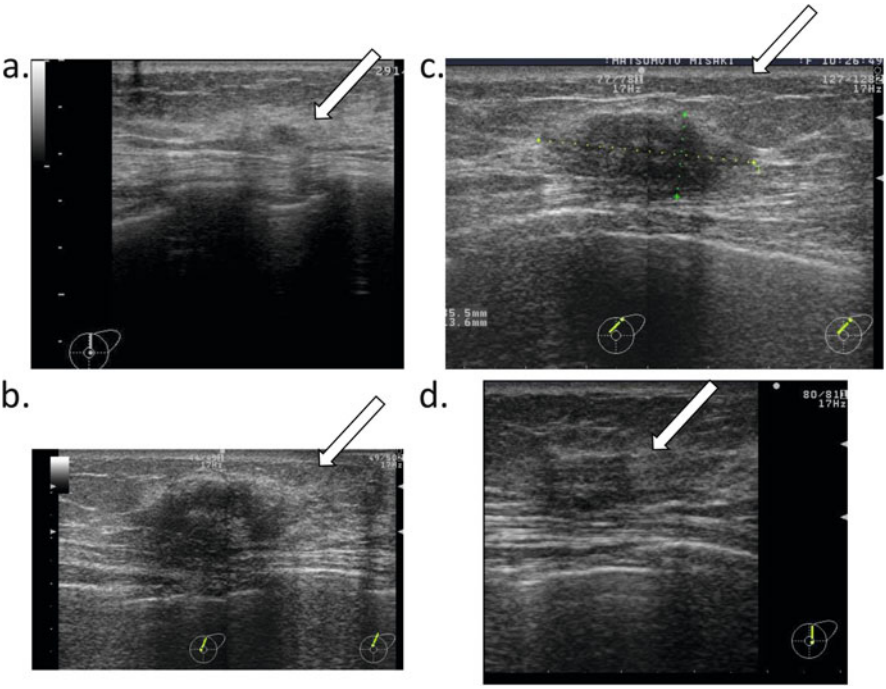

Fig. 18.17 Serial changes of ultrasonography after cryoablation. (**a**) Preoperative ultrasonography: the lesion was indicated with *white arrow*. (**b**) Six months after cryoablation: granulation was indicated with *white arrow*. (**c**) Fifteen months after cryoablation: Granulation is smaller than at 6 months. (**d**) Forty-seven months after cryoablation: granulation was smaller than at 15 months but still there

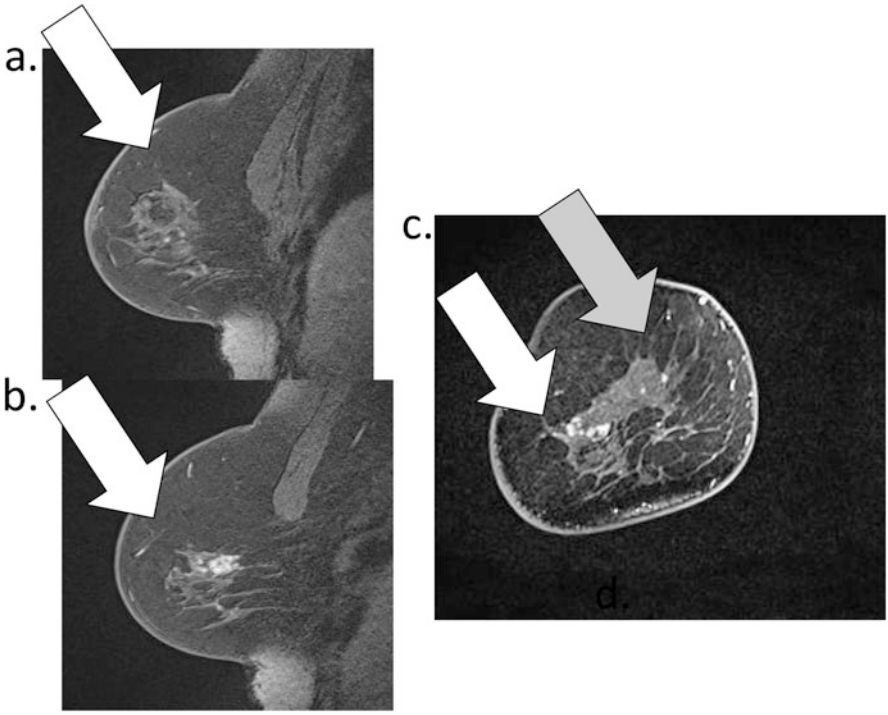

Fig. 18.18 IBTR after nonsurgical cryoablation with breast MRI. (**a**) Ablated area (*white arrow*) on sagittal section. (**b**) IBTR (*white arrow*) in right outer region on sagittal section. (**c**) IBTR (*grey and white arrow*) was caudal to ablated area on coronal section

18.9 Rationale of Cryoablation and Comparison with Breast Conservative Surgery

Small breast cancer, which is less than 10 mm as lesion size, Luminal A and sentinel node negative, is known as a favorable type of breast cancer. Local control with breast conservative surgery is expected to have a low IBTR rate. The IBTR rate after breast conservative surgery is less than 1% at our institution. One patient developed IBTR among 150 patients with nonsurgical cryoablation and this result of the procedure is comparable with that of breast conservative surgery (Fig. 18.17). No thermal injury to the patients has been observed.

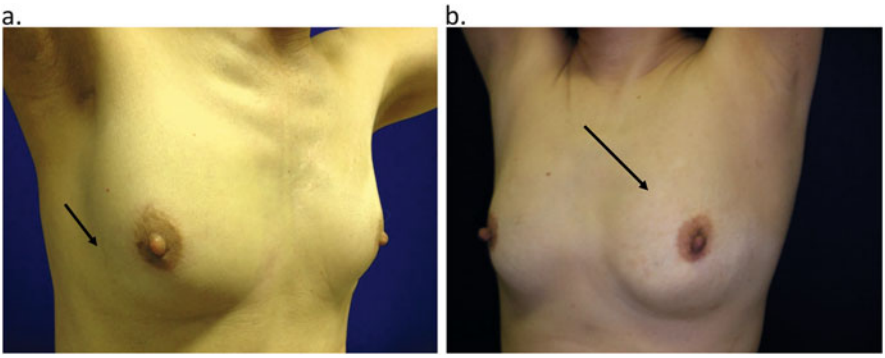

Fig. 18.19 Cosmetic effect after nonsurgical cryoablation for small breast cancer. (**a**) Thirty-two months after cryoablation in marginal area of right lower outer quadrant. (**b**) Fifty-nine months after cryoabaltion in left upper inner quadrant

18.10 Cosmetic Outcome and Long-Term Results

Cosmetic outcome after nonsurgical cryoablation is excellent (Fig. 18.19). Although induration caused by destroying the lesion and normal breast tissue is palpable for a longer time period, its size grows gradually smaller. In most patients, induration is palpable less than index finger tip size.

18.11 Conclusion

Nonsurgical cryoablation is comparable local treatment with conservative breast surgery for favorable-type small breast cancer and expansion of indication should be followed in the near future.

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