

Unresected Breast Cancer: Evolution of Imaging Findings Following Cryoablation

Jennifer T. Bergin, M.D., Gale A. Sisney, M.D., Fred T. Lee, Jr., M.D., Elizabeth S. Burnside, M.D., and Lonie R. Salkowski, M.D.

Cryoablation has been used to treat both benign and malignant breast tumors. In all but one published case, cryoablation in breast cancer has been followed by post-procedural tumor resection. We present a case of an 85-year-old woman with two nonpalpable breast cancers treated with cryoablation with 18 months of mammographic, ultrasound and histologic follow-up.

Introduction

The use of freezing temperatures to kill tumors dates back to the 1800s when Dr. James Arnott applied salt and ice mixtures to breast, skin and uterine cancers. He observed a reduction in local hemorrhage, pain, odor, discharge, and tumor size [1]. The modern age of cryoablation began in the 1960s when Dr. Irving S. Cooper developed the first closed cryoprobe that circulated cold nitrogen gas, allowing him to freeze the thalamus in patients with Parkinson's Disease [2].

In the 1980s and 1990s two key developments occurred, leading to an explosion in the applications of

cryoablation. First, Dr. Gary Onik noted the echogenic nature of the iceball on ultrasound, leading to the first percutaneous cryoablation procedures. Then, in 1999, Dr. Fred Lee and colleagues published results of a pilot study using cryoablation with CT guidance [3]. They noted superb visualization of the iceball, allowing precise treatment with minimal collateral tissue damage.

Recently, cryoablation has been used to treat both benign and malignant breast tumors. A multicenter trial using cryoablation to treat fibroadenomas in an outpatient setting with local anesthesia demonstrated great success. The procedure was safe and effective with only mild complications. The median reduction in tumor volume was greater than 91% and patients expressed satisfaction with the procedure [4,5,6].

The efficacy of cryoablation in the treatment of malignant breast disease is also documented in the literature [7,8,9,10]. The results of the first multi-institutional trial of cryoablation followed by resection showed that all tumors smaller than 1 cm in size were fully ablated. Tumors from 1 to 1.5 cm without an extensive extraductal component were also fully ablated. The majority of tumors larger than 1.5 cm were also fully ablated, though several demonstrated residual disease at the periphery of the ablation zone. Sabel et al concluded that cryoablation of primary breast cancer is safe and effective, but should be

Citation: Bergin JT, Sisney GA, Lee FT, Burnside ES, Salkowski LR. Unresected Breast Cancer: Evolution of Imaging Findings Following Cryoablation. *Radiology Case Reports*. [Online] 2008;3:150.

Copyright: © 2008 by Jennifer T. Bergin, M.D. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs 2.5 License, which permits reproduction and distribution, provided the original work is properly cited. Commercial use and derivative works are not permitted.

Abbreviations: CC, craniocaudal; CT, computed tomography; DCIS, ductal carcinoma-in-situ; MRI, magnetic resonance imaging

Jennifer T. Bergin, M.D. (Email: jbergin@uwhealth.org), Gale A. Sisney, M.D., Fred T. Lee, Jr., M.D., Elizabeth S. Burnside, M.D., and Lonie R. Salkowski, M.D., are in the Department of Radiology, University of Wisconsin Hospital and Clinics, Madison, WI, USA.

Published: February 11, 2008

DOI: 10.2484/rcc.v3i1.150

Unresected Breast Cancer: Evolution of Imaging Findings Following Cryoablation

limited to invasive carcinomas smaller than 1.5 cm with less than 25% DCIS on the core biopsy [9].

In all but one published case, cryoablation in breast cancer has been followed by post-procedural tumor resection [11].

Case Report

An 85-year-old woman presented to our breast center with two nonpalpable masses in her right breast detected on screening mammogram. Subsequent diagnostic mammography and sonography confirmed two masses in the right breast at 2 and 4 o'clock. The posterior mass at 2 o'clock measured 7 x 6 mm while the 4 o'clock mass measured 6 x 6 mm. (Figures 1 and 2). Ultrasound-guided core biopsies and post-procedure clip placement had been performed of both masses at an outside institution. Pathology showed grade 1 invasive ductal carcinoma with low grade DCIS in the 2 o'clock lesion and grade 2 invasive ductal carcinoma in the 4 o'clock lesion. The patient refused surgical treatment, radiation therapy, chemotherapy, chemoprevention therapy, and breast MRI. She was amenable to cryoablation, with the understanding that there was no proven benefit of cryoablation in the breast.

The patient was treated as an outpatient at our breast center by two radiologists (GAS, FTL) with extensive experience with percutaneous breast procedures and over 12 years experience in interventional oncology procedures.

Informed consent was obtained. Following routine sterile preparation, buffered 1% lidocaine was injected subcutaneously for local anesthesia. The patient received 0.5 mg Midazolam and 50 micrograms Fentanyl for sedation. Two 3 mm incisions were made in the medial right breast. With ultrasound guidance, a 1.7 mm diameter cryoprobe (Endocare, Irvine, California, USA) was placed into the center of each mass for simultaneous treatment. The tips of the probes were positioned 3 mm distal to the tumors. A short freeze cycle was used to freeze the probes in position. Then, a 10-minute freeze cycle was applied followed by a passive 5-minute thaw and a second 10-minute freeze. The freeze temperatures achieved were at least -140 degrees centigrade. The iceball formation was monitored continuously with ultrasound. At the completion of the second freeze cycle, an active 10-minute thaw was initiated and the probes were removed. Pressure was applied to the entry sites for approximately 5 minutes and Band-Aids were applied. The patient was observed in the radiology recovery area for 2 hours prior to discharge home. She tolerated the procedure well with no significant pain or complication.

Both tumors were successfully cryoablated. During the procedure ice balls completely encased the tumors and approximately a 1 cm margin of adjacent tissue in all directions. At two hours post-ablation, the ice balls had resolved, leaving small indistinct areas of decreased echogenicity that were thought to represent the residual tumors and surrounding tissue at each site.

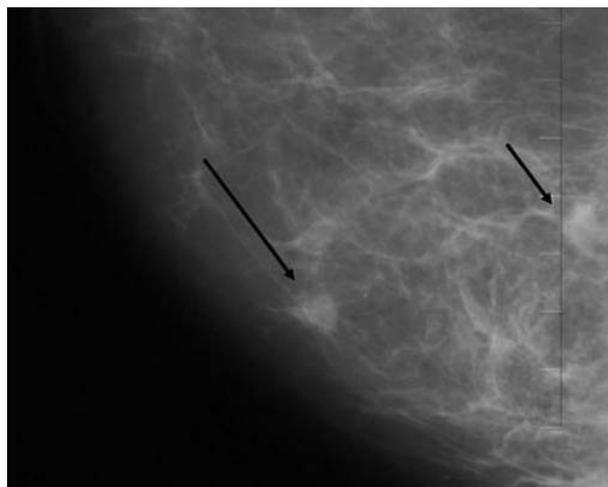


Figure 1. CC view from the diagnostic mammogram demonstrates two ill-defined, spiculated masses, each smaller than 1 cm. The 2 o'clock mass is posterior (short arrow) and the 4 o'clock mass is anterior (long arrow).



Figure 2. Post-biopsy and pre-ablation sonogram demonstrates a hypoechoic, shadowing mass at 2 o'clock with a central biopsy clip (white arrow). The 4 o'clock mass had a similar sonographic appearance.

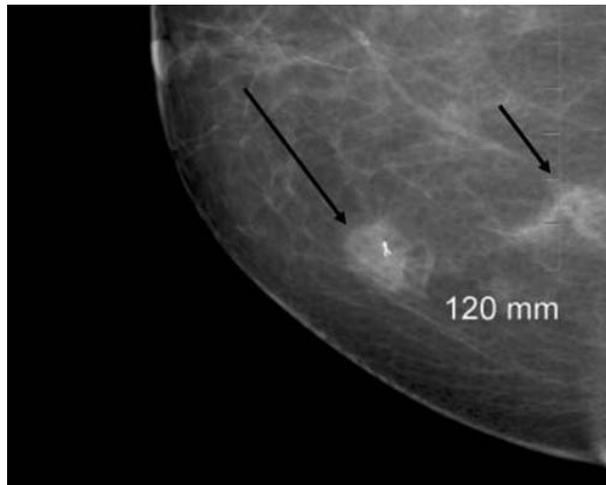


Figure 3. 6 months after cryoablation, the diagnostic mammogram CC view demonstrates similar changes at both the 2 o'clock (short arrow) and 4 o'clock (long arrow) sites. The halo of density at each site is decreased compared to the immediate post-ablation appearance. At 2 o'clock, the central mass is no longer seen, while at 4 o'clock the central mass continues to decrease in size and appears less defined.

At six weeks post-ablation, the patient returned for sonography and mammography. The mammogram demonstrated the posterior 2 o'clock lesion with a biopsy clip in the center of an irregular mass. A halo of soft tissue density surrounded the mass. Similarly, there was a biopsy clip in the center of the 4 o'clock mass with a surrounding halo of density. Sonography showed an irregular hypoechoic central area with an approximately 1 cm hyperechoic rim at each site. Biopsy clips were seen centrally in both lesions.

Three months after ablation, the irregular mass at 2 o'clock was more lucent on mammography. A halo of surrounding density persisted. At 4 o'clock identical changes were noted. Sonography showed increasingly indistinct borders to the hypoechoic central areas. The hyperechoic rims were less prominent, corresponding with the resolving mammographic densities at each site.

On the mammogram at six months post-ablation, the irregular mass at 2 o'clock was no longer seen (Figure 3). The halo of density was also significantly decreased. At 4 o'clock the irregular mass was less prominent and there was slightly decreased surrounding density. Sonographic findings correlated with further interval decrease in the hyperechoic rims. The hypoechoic central areas decreased in size as well at each site (Figure 4).

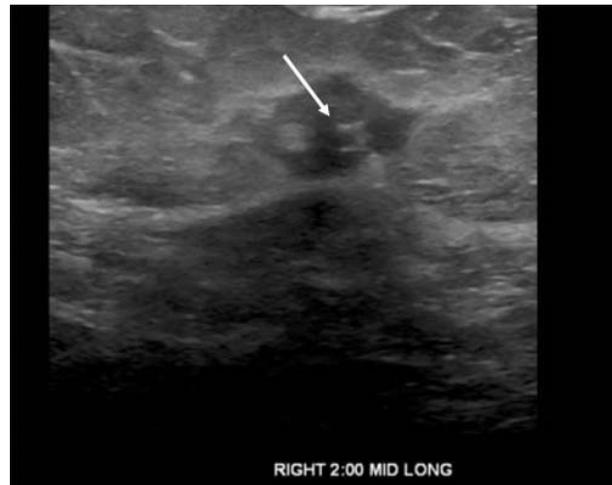


Figure 4. Sonogram at 6 months after cryoablation demonstrates the 2 o'clock mass as a poorly defined hypoechoic area with a central biopsy clip (white arrow). The halo of increased density noted immediately after cryoablation has resolved.

Mammography one year after cryoablation showed the biopsy clips with no definite residual mass at either site (Figure 5). There was minimal residual surrounding density without architectural distortion or new calcification. Without the aid of the biopsy clips, the lesions would have been difficult to locate on ultrasound. Both hyperechoic rims had resolved (Figure 6).

At eighteen months post-ablation, the patient returned for a follow-up diagnostic mammogram and sonogram. The biopsy clips were again noted with no residual mass at either site. There was no density, architectural distortion, or calcification at the 2 o'clock site. There was minimal residual surrounding density at the 4 o'clock anterior site with no architectural distortion or calcification. A new 8 mm high density mass was noted at 3 o'clock, between the 2 o'clock and 4 o'clock sites of prior cryoablation, but separated from them by at least 2 cm on mammography. The mass demonstrated irregular margins (Figure 7).

On ultrasound, the two sites of prior cryoablation appeared similar to the twelve month follow-up with indistinct hypoechoic areas noted around the biopsy clips. A new mass was seen correlating with the mammographic findings. The mass was hypoechoic and microlobulated, measuring 9 mm in greatest dimension (Figure 8).

An ultrasound-guided core biopsy was recommended for the new mass. This was performed with a 9-gauge Suros vacuum assisted biopsy device. At the same time, the

Unresected Breast Cancer: Evolution of Imaging Findings Following Cryoablation

patient consented to biopsy of the prior cryoablation sites. At each of the two sites, the biopsy needle was placed in the center of the cryoablation site, guided by the marker clips. New marker clips were placed at each of the three sites and a mammogram was performed to confirm clip placement. The post-biopsy mammogram demonstrated three separate marker clips with interval removal of the two old clips at 2 and 4 o'clock.

Pathology of the new 3 o'clock mass demonstrated infiltrating ductal carcinoma (Bloom Richardson grade 1) with a small (0.5 mm) focus of low grade DCIS. Results from the 2 o'clock site of cryoablation showed benign breast tissue. At the 4 o'clock site a small focus (0.5 mm) of low grade DCIS was noted with reparative changes of prior biopsy.

Discussion

The post-treatment mammography and sonography in our patient demonstrated changes similar to those described in cryoablated benign breast tissue of an animal model and cryoablated fibroadenomas [7,12]. Mammography showed gradual lesion resorption with decreasing density. Sonography revealed ill-defined central masses with hyperechoic rims that slowly resolved. There was no calcification or architectural distortion to complicate

post-procedural image interpretation. When compared to surgery, the sequelae of cryoablation using mammographic and sonographic criteria are significantly decreased. This may translate into improved detection of tumor recurrence in breast cancers treated with cryoablation versus surgery, where published data demonstrates decreased sensitivity of mammography due to surgery and radiation-related changes in the breast parenchyma [13,14,15].

The occurrence of a new cancer in our patient 18 months after initial cryoablation of two separate disease foci does not appear to be a failure of cryoablation. This new focus of disease was separated from the 2 o'clock site by 3 cm and from the 4 o'clock site by 2 cm on mammography.

The presence of noncalcified DCIS in the core biopsy performed 18 months after cryoablation at the 2 o'clock site points to one of the greatest challenges facing ablative therapies in the breast. Existing literature regarding cryoablation of breast carcinoma indicates that the presence of an extensive (greater than 25%) intraductal component should exclude the patient from percutaneous cryoablation [8,9,10,11]. With present imaging techniques, it may be difficult to identify these patients. Mammography shows microcalcifications forming in DCIS [16,17]. However, mammography is inaccurate at predicting the extent of disease if only a portion of the malignancy is calcified [18]. Sonography is similarly inaccurate at determining the pres-

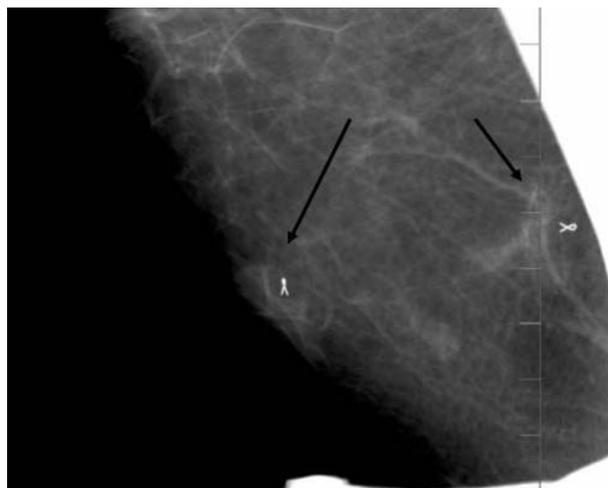


Figure 5. CC view mammogram obtained 12 months after treatment shows the central masses have resolved at both the 2 o'clock (short arrow) and 4 o'clock (long arrow) sites. There is minimal surrounding density with no architectural distortion or calcification.



Figure 6. Sonogram at the 2 o'clock position 12 months after cryoablation shows the site is difficult to locate except for the marker clip (white arrow). A very poorly defined area of decreased echogenicity is noted.

Unresected Breast Cancer: Evolution of Imaging Findings Following Cryoablation

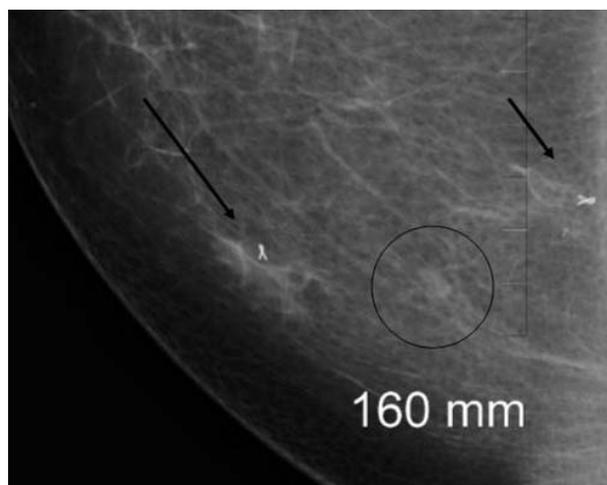


Figure 7. 18 months after cryoablation, the 2 o'clock (short arrow) and 4 o'clock (long arrow) sites are unchanged in appearance with no residual or recurrent mass at either site. A new 8 mm mass is present at 3 o'clock (circle).



Figure 8. Sonogram at the 2 o'clock position 18 months after cryoablation shows the biopsy clip at 2 o'clock (white arrow) with a poorly defined area of surrounding hypoechoogenicity.

ence and extent of an intraductal component [19].

Overall, the results regarding MRI in the evaluation of DCIS have been modest, with published series showing MRI sensitivities for DCIS as low as 40% and as high as 100% [20,21,22,23,24]. MRI does not dependably show the classic microcalcifications that form in DCIS and DCIS may show delayed or even no contrast enhancement on MRI [18,20]. Thus, the addition of MRI to the evaluation of potential cryoablation patients is useful, but somewhat limited in its sensitivity for DCIS.

The tumors in our case were easily encompassed with the iceballs generated by the 1.7 mm probes used, with ultrasound demonstrating an approximate 1 cm margin of ablated tissue in all directions around the tumors. Published series suggest a size limitation of 1.5 cm, with incomplete ablation occurring in larger tumors [8,10]. This limitation is largely due to the type of cryoprobe used. All published cases to date report the use of single probes. A single 1.7 mm probe produces an iceball approximately 3 cm in diameter. If positioned centrally in a 1 cm tumor, the single probe would ablate the tumor and provide margins of approximately 1 cm. Elsewhere in the body and in fibroadenomas, multiple probes have been used in a single lesion with success [5,25]. With proper probe placement, a multi-probe technique could be similarly successful in breast malignancies.

Another challenge facing in situ breast cancer ablation

is determination of treatment margins. The post-ablation core biopsy of the 2 o'clock site showed DCIS, even though there was no evidence of DCIS on the pre-ablation core biopsy. This DCIS may have been present at the time of initial treatment. If so, it likely would have been identified on wide excision and tumor-free margins obtained. Pathologic margin status is one of the most important predictors for local recurrence [26,27]. The use of MRI for ablation planning and follow-up should be helpful. At our institution, following hepatic radiofrequency ablation, a contrast enhanced CT is performed immediately after the ablation session to evaluate for residual enhancement. If enhancement persists at the margins, there is presumed residual tumor and additional ablation is performed, typically within the same ablation session. A similar strategy could be applied to cryoablation in the breast with evaluation for residual gadolinium enhancement on MRI. Furthermore, MR guidance may prove to be a more accurate imaging modality for monitoring and guidance of cryoablation. Tumor and frozen tissue are well differentiated on MRI and MRI provides delineation of the iceball in three-dimensions, an advantage over ultrasound [28].

Several thermal ablation techniques are currently under evaluation for use in the breast. A discussion of all the different ablative modalities is beyond the scope of this case report. However, cryoablation is unique in its use of hypothermia. While hyperthermic ablative processes dena-

Unresected Breast Cancer: Evolution of Imaging Findings Following Cryoablation

ture proteins and fuse cell membranes, cryoablation leaves tumor specific antigens and proteins intact. In the inflammatory post-ablation environment, the intact tumor antigens can stimulate an anti-tumor immune response [29]. Work with a murine model demonstrates that cryoablation is superior to surgical excision in stimulating T-cell and natural killer cell activity and in significantly reducing the tumor recurrence rate after rechallenge [30].

Many questions remain unanswered regarding the use of cryoablation in breast cancer. However, this case supports the findings already in the literature regarding the safety and efficacy of cryoablation in small tumors. In the future, cryoablation with adjuvant therapy may be an accepted alternative treatment for minimal (smaller than 1 cm) invasive breast cancers, resulting in lower patient morbidity and greater patient satisfaction. A clinical trial of cryoablation with and without tumor resection is needed. Additional work should be done in margin assessment, imaging follow-up and non-invasive determination of nodal status.

References

1. Arnott J. Practical illustrations of the remedial efficacy of a very low or anesthetic temperature. *Lancet* 1850; 2:257-259.
2. Cooper IS. A cryogenic method for physiologic inhibition and production of lesions in the brain. *J Neurosurg* 1962; 19:853-858. [PubMed]
3. Lee FT Jr, Chosy SG, Littrup PJ, Warner TF, Kuhlman JE, Mahvi DM. CT-monitored percutaneous cryoablation in a pig liver model: pilot study. *Radiology* 1999;211 : 687-692. [PubMed]
4. Littrup PJ, Freeman-Gibb L, Andea A, White M, et al. Cryotherapy for breast fibroadenomas. *Radiology* 2005; 64:63-72. [PubMed]
5. Caleffi M, Duarte Filho D, Borghetti K, Graudenz M, et al. Cryoablation of benign breast tumors: evolution of technique and technology. *The Breast* 2004; 13:397-407. [PubMed]
6. Kaufman CS, Bachman B, Littrup PJ, et al. Cryoablation treatment of benign breast lesions with 12-month follow-up. *The American Journal of Surgery* 2004; 188:340-348. [PubMed]
7. Roubidoux MA, Sabel MS, Bailey JE, et al. Small (<2.0-cm) breast cancers: mammographic and US findings at US-guided cryoablation--initial experience. *Radiology* 2004; 233:857-867. [PubMed]
8. Sabel MS, Kaufman CS, Whitworth P, Chang H, et al. Cryoablation of early-stage breast cancer: work-in-progress report of a multi-institutional trial. *Ann Surg Oncol* 2004; 11:542-549. [PubMed]
9. Pfeiderer SOR, Freesmeyer MG, Marx C, Kuhne-Heid R, Schneider A, Kaiser WA. Cryotherapy of breast cancer under ultrasound guidance: initial results and limitations. *Eur Radiol* 2002; 12:3009-3014. [PubMed]
10. Pfeiderer SOR, Marx C, Camara O, et al. Ultrasound-guided, percutaneous cryotherapy of small (<2.0cm) breast cancers. *Invest Radiol* 2005; 40:472-477. [PubMed]
11. Staren ED, Sabel MS, Gianakakis LM, et al. Cryosurgery of breast cancer. *Arch Surg* 1997; 132(1);28-33. [PubMed]
12. Otterson MF, Redlich PN, McDonald A, Thorsen MK, Klaas KK, Clowry LJ, Walker AP. Sequelae of cryotherapy in breast tissue. *Cryobiology* 2003; 47:174-178. [PubMed]
13. Giess CS, Keating DM, Osborne MP, Rosenblatt R. Local tumor recurrence following breast-conservation therapy: correlation of histopathologic findings with detection method and mammographic findings. *Radiology* 1999; 212:829-835. [PubMed]
14. Dershaw DD. Mammography in patients with breast cancer treated by breast conservation (lumpectomy with or without radiation). *AJR* 1995; 164:309-316. [PubMed]
15. Orel SG, Troupin RH, Patterson EA, Fowble BL. Breast cancer recurrence after lumpectomy and irradiation; role of mammography in detection. *Radiology* 1992; 183:201-206. [PubMed]
16. Dershaw DD, Abramson A, Kinne DW. Ductal carcinoma in situ: mammographic findings and clinical implications. *Radiology* 1989; 170:411-415. [PubMed]
17. Lagios MD, Westdahl PR, Margolin FR, Rose MR. Duct carcinoma in situ. Relationship to extent of nonin-

Unresected Breast Cancer: Evolution of Imaging Findings Following Cryoablation

vasive disease to the frequency of occult invasion, multicentricity, lymph node metastases, and short-term treatment failures. *Cancer* 1982; 50:1309-1314. [PubMed]

18. Holland R, Hendriks JH, Vebeek AL, Mravunac M, Schuurmans Stekhoven JH. Extent, distribution, and mammographic/histological correlations of breast ductal carcinoma in situ. *Lancet* 1990; 335:519-522. [PubMed]

19. Tresserra F, Feu J, Grases PJ, et al. Assessment of breast cancer size: sonographic and pathologic correlation. *J Clin Ultrasound* 1999; 27:485-491. [PubMed]

20. Harms SE, Flamig DP, Hesley KL, Meiches MD, Jensen RA, Evans WP, et al. MR imaging of the breast with rotating delivery of excitation off resonance: clinical experience with pathologic correlation. *Radiology* 1993; 18:493-501. [PubMed]

21. Heywang-Kobrunner SH. Contrast-enhanced magnetic resonance imaging of the breast. *Invest Radiol* 1994; 29:94-104. [PubMed]

22. Gilles R, Zafrani B, Guinebretiere JM, Meunier M, Lucidarme O, Tardivon AA, et al. Ductal carcinoma in situ: MR imaging-histopathologic correlation. *Radiology* 1995; 196:415-419. [PubMed]

23. Orel SG, Mendonca MH, Reynolds C, Schnall MD, Solin LJ, Sullivan DC. MR imaging of ductal carcinoma in situ. *Radiology* 1997; 202:413-420. [PubMed]

24. Soderstrom CE, Harms SE, Copit DS, Evans WP, Savino DA, Krakos PA, et al. Three-dimensional RODEO breast MR imaging of lesions containing ductal carcinoma in situ. *Radiology* 1996; 201:42-432. [PubMed]

25. Hinshaw JL, Lee FT Jr. Cryoablation for liver cancer. *Tech Vasc Interv Radiol* 2007; 10(1):47-57. [PubMed]

26. Chagpar A, Yen T, Sahin A, et al. Intraoperative margin assessment reduces reexcision rates in patients with ductal carcinoma in situ treated with breast-conserving surgery. *Am J Surg* 2003; 186:371-377. [PubMed]

27. Singletary SE. Surgical margins in patients with early stage breast cancer treated with breast conservation therapy. *Am J Surg* 2002; 184:383-393. [PubMed]

28. Morin J, Traore A, Dionne G, et al. Magnetic resonance-guided percutaneous cryosurgery of breast carcinoma: technique and early clinical results. *Can J Surg* 2004; 47:347-351. [PubMed]

29. Johnson JP. Immunologic aspects of cryosurgery: potential modulation of immune recognition and effector cell maturation. *Clinics in Dermatology* 1990; 8:39-44. [PubMed]

30. Sabel MS, Nehs MA, Su G, Lowler KP, et al. Immunologic response to cryoablation of breast cancer. *Br Cancer Research and Treatment* 2005; 90:9-104. [PubMed]