



## CRYOABLATION FOR THE TREATMENT OF BREAST FIBROADENOMAS

### *A Technology Review*

#### INTRODUCTION

The California Technology Assessment Forum has been asked to review the scientific literature on the safety and efficacy of cryoablation for the treatment of breast fibroadenomas.

#### BACKGROUND

##### Breast Fibroadenomas

The lifetime risk for fibroadenomas is about 10%. Most are discovered during clinical breast examinations or by patient self-breast examination. Approximately 1.4 million breast biopsies are performed annually in the United States; between 30% and 75% of the masses are identified fibroadenomas.<sup>1</sup>

The management of fibroadenomas is controversial. Historically, excisional biopsy has been the treatment of choice. This allows for definitive diagnosis of the mass and allays patient anxiety. However, most authors believe that it is not necessary to excise all fibroadenomas. Since fibroadenomas are a common finding, many women would be at risk for damage to the ducts and a possible poor cosmetic outcome. Fibroadenomas are particularly common in younger women. The natural history is that the majority of lesions regress<sup>2</sup>, with only a minority increasing in size over follow-up.<sup>3, 4</sup> Recently, many experts recommend follow-up with serial ultrasounds.<sup>5, 6</sup> Excision is necessary only for fibroadenomas that increase in size during follow-up. In spite of this, many women elect excision because of anxiety about the lesion.

Complications of excisional surgery include scarring at the incision site, dimpling of the breast due to the volume of tumor removed, damage to the ductal system and increased mammographic density at the excision site due to parenchymal scar.

##### Cryoablation

Cryoablation has been proposed as a less invasive alternative to excisional biopsy with improved cosmetic results and high patient satisfaction.

Cryoablation destroys tissue locally by repeating freeze thaw cycles. At least three mechanisms are thought to be responsible for local tissue necrosis. These include intracellular ice formation which damages cell

membranes, osmotic injury due to increasing solute concentration and disruption of local microcirculation leading to ischemic damage.<sup>7</sup> Several studies have demonstrated uniform necrosis to tissue exposed to two freeze-thaw cycles at -40° C.<sup>8-10</sup>

The procedure is performed under ultrasound guidance usually under local anesthesia. A cryoprobe is placed percutaneously into the center of the fibroadenoma. Based on the size of the lesion, parameters are chosen to completely surround the fibroadenoma in frozen tissue. Two freeze thaw cycles are generally used.

Possible harms include local swelling and ecchymosis after the procedure. Rarely, breast cancer present within the fibroadenoma may be missed. It is unclear whether cryoablation of local breast cancer would result in similar outcomes as excisional biopsy with appropriate staging and treatment of the cancer.

<b>TA Criterion 1: Does the technology have final approval from the appropriate government regulatory bodies?</b>		
<b>Criterion Met?</b>	<b>Evidence</b>	<b>Summary</b>
TA Criterion 1 is met	FDA clearance	<p>510K The Sanarus Visica™ Treatment System (Sanarus Medical, Inc., Pleasanton, CA) received FDA 510K approval on November 15, 2005. This approval is based on the predicate Sanarus Visica Treatment System approved by the FDA in 2002.</p> <p>The SeedNet Family of Cryosurgical units (Galil Medical Ltd, Israel) which includes SeedNet/SeedNetGold System, CryoThera System, and the Cryo-Hit System, received FDA 510K approval for expanded use in the treatment of breast fibroadenomas on November 18, 2005.</p>
<b>TA Criterion 2: Does the Scientific Evidence permit conclusions concerning the effectiveness of the technology regarding health outcomes?</b>		
<b>Criterion Met?</b>	<b>Evidence</b>	<b>Summary</b>
TA Criterion 2 is not met.	Level 5 evidence only  Evidence is insufficient to evaluate clinical efficacy of a new technology.	<p>The search identified seven articles describing overlapping series of patients from three uncontrolled case-series.<sup>1, 11-16</sup> Several of the articles report only the total number of treated lesions and not the number of treated patients. Other series include other benign breast tumors such as fibrocystic changes.<sup>11, 14</sup> The largest series reported on 444 lesions, but follow-up was incomplete with fewer than 20% of lesions evaluated at 12 months.<sup>16</sup> None of the case-series document the systematic use of any validated instrument to establish patient satisfaction, adverse events or to evaluate any other outcomes. Follow-up was grossly inadequate to report intermediate length follow-up. For instance in 2002, Kaufman et al reported a median tumor volume reduction of 92% even though this was based on just three patients with one year follow-up in the study.<sup>1</sup> This result was cited in several subsequent articles to substantiate the efficacy of the procedure.<sup>17</sup> In the 2004 report of the same case series, Kaufman</p>

et al. noted that they excluded their failures from analyses at one year thus by design they include only patients with good outcomes.<sup>14</sup> This clearly introduces large biases in the study results.

**TA Criterion 3: Does the technology improve net health outcomes?**

Criterion Met?	Evidence	Summary
TA Criterion 3 is not met		<p>The data from the case series are summarized in the Table. The first four articles appear to refer largely to the same patients. <sup>1, 11, 13, 14</sup> The data suggest that there is a significant reduction in the size of the lesions at one year with the majority of patients (92% of the 54 patients with 12 month follow-up) reporting good or excellent results. Most patients experienced local pain and swelling, one developed a breast abscess, two formed keloids, and two had persistent skin depigmentation.</p> <p>The larger registry data<sup>12, 16</sup> suggested that outcomes, while good, may not be as optimistic as those in the initial reports. Almost half of the treated lesions were still palpable at six months and more than a third were palpable at 12 months follow-up. One fourth of the women reported residual pain at the biopsy site at 12 months. The rate of hematoma formation was 4% and the infection rate was 2%. Because the studies did not include concurrent controls receiving surgical excision or watchful waiting, it is difficult to assess whether cryoablation improves net health outcomes in any population.</p>

**TA Criterion 4: Is the technology as beneficial as any established alternatives?**

Criterion Met?	Evidence	Summary
TA Criterion 4 is not met.	No comparative trials.	There are many alternatives to cryoablation including watchful waiting with serial ultrasounds, excisional biopsy, vacuum assisted biopsy and a variety of technologies relying on local heating of tissue (radiofrequency, laser, focused ultrasound, microwaves). No studies directly comparing cryoablation to any alternative were identified. Thus, it is impossible to evaluate whether cryoablation is as beneficial as any established alternative.

**TA Criterion 5: Is the improvement attainable outside the investigational setting?**

Criterion Met?	Evidence	Summary
TA Criterion 5 is not met	Registry data with 55 centers in community.	The FibroAdenoma Cryoablation Treatment Registry is evaluating the efficacy of cryoablation in a broad range of practice settings with a large number of individual clinicians. It appears feasible to train physicians to perform this procedure outside of the investigational setting. However, no standards for training have been established. Moreover, no improvements have been demonstrated in the investigational setting..

## CONCLUSION

Seven articles have been published describing overlapping data from three case series. The data suggest that most patients are satisfied with the results even though there is a high risk for local pain and swelling in the post-procedure period and a low risk for infection, long term pain, and mild cosmetic defects. Unfortunately, there are no comparative studies in the literature. The current recommendation for management of most fibroadenomas is watchful waiting with periodic ultrasound evaluation. It is unclear if cryoablation is being advocated as an alternative to observation or an alternative to excisional biopsy. Women who are very anxious about the presence of a benign tumor or who have enlarging masses are often referred for excisional biopsy. Ideally, women who prefer immediate treatment to watchful waiting would be randomized to either surgical excision or cryoablation. Standardized assessments of pain, anxiety, patient satisfaction and cosmetic results could be assessed by a blinded outcome assessor at standard intervals. Adverse events could also be compared between the two groups. Such a study would help to define the role of cryoablation in the management of fibroadenomas.

## Recommendation

Criteria Met?	Evidence	Summary
Criteria 2 through 5 are not met.	Poor Level 5	It is recommended that the use of the cryoablation for the treatment of breast fibroadenomas does not meet Technology Assessment Criterion 2 through 5 for safety, effectiveness and improvement in health outcomes.

*The California Technology Assessment Forum panel voted to approve the recommendation.*

*February 15, 2006*

**Table: Studies of cryoablation of breast fibroadenomas**

Study	Patients, n	Lesions, n	Volume reduction, %	Patient satisfaction, %	Complications
Kaufman 2002	50 Age 35 (SD 13) years Physical exam, mammogram, ultrasound, core biopsy.	57 Size 2.1 (range .8-4.2) cm Tumors other than fibroadenomas included.	6-month data on 20 patients: 65% mean reduction in volume. 3 patients at 12 months with 92% reduction in volume.	"Patients were highly satisfied with the procedure."	All with local swelling and ecchymosis that resolved within three weeks. Small residual scar similar to core biopsy scar. Several rashes to tape. No other complications.
Kaufman 2004  Likely includes all patients in Kaufman 2002 article	<63 Age 34 (13-66)	66 Size 2.0 (SD .8) cm Tumors other than fibroadenomas included.	87% in 53 lesions with one-year follow-up. 14 patients excluded: 4 inadequate freezing time; 4 inaccurate probe placements; 1 probe failure; 5 lost to follow-up.	Good to excellent in 92% of patients with 12-month follow-up. 2 patients had surgical excision.	All with local swelling and ecchymosis that resolved within three weeks. 3 patients with moderate pain resolving within one week. Tape blisters: 9 at six weeks, 2 at 12 months. Skin depigmentation: 6 at six weeks, 2 at 12 months. Keloid: 2 at 12 months. Breast abscess: 1.

Study	Patients, n	Lesions, n	Volume reduction, %	Patient satisfaction, %	Complications
<p>Caleffi 2004</p> <p>70 fibroadenomas in Tailored Freeze cohort may be same patients reported in the two Kaufman papers above.</p>	<p>102</p> <p>Age 38 years.</p> <p>Lesion visible on ultrasound, biopsy proven to be benign. Excluded if history of ipsilateral breast cancer. Approximately 85% are fibroadenomas.</p>	<p>124</p> <p>Tumors other than fibroadenomas included.</p>	<p>91% in 54 patients with 68 tumors including 57 fibroadenomas had 12-month outcome data.</p>	<p>Good to excellent in 92% of the 54 patients with 12-month data.</p> <p>2 patients had surgical excision of continued palpable fibroadenomas after 12 months.</p>	<p>For Tailored Freeze protocol:</p> <p>Ecchymosis, discomfort and edema commonplace.</p> <p>Severe pain: 2</p> <p>Hematomas: 4</p> <p>Breast abscess: 1</p> <p>Hypopigmentation at 12 months: 2</p>
<p>Kaufman 2005</p> <p>? Included above.</p>	<p>Unclear</p>	<p>37</p> <p>84% palpable</p>	<p>NR</p> <p>16% palpable after 2.6 years follow-up.</p>		
<p>Edwards 2004</p>	<p>Unclear</p>	<p>310</p> <p>Size 1.8 cm</p> <p>77% palpable</p>	<p>97% based on 12 patients at one year.</p> <p>51% based on 89 patients at 6 months.</p> <p>50% of tumors palpable at 6 months.</p>	<p>100% at one year based on 12 patients (4% one year follow-up).</p> <p>92% satisfied at 6 months based on 89 patients (&lt;35% follow-up at 6 months).</p>	<p>78% required over the counter analgesics alone, unclear if 22% required prescription analgesics.</p> <p>4% (10/250) with hematomas.</p> <p>41% (106/250) with ecchymosis.</p> <p>2% infection.</p>

<b>Study</b>	<b>Patients, n</b>	<b>Lesions, n</b>	<b>Volume reduction, %</b>	<b>Patient satisfaction, %</b>	<b>Complications</b>
Nurko 2005  Same cohort as Edwards 2004.	Unclear  Tissue diagnosis of fibroadenoma.	444  Size 1.8 cm  75% palpable	% reduction in size not reported.  46% (110/237) palpable at 6 months, 35% (29/82) palpable at one year.	91% (216/235) satisfied at 6 months and 88% (74/84) at 12 months.	Residual pain at biopsy site in 15% (37/242) at 6 month and in 25% (22/87) at 12-month follow-up.
Littrup 2005	29  Age 27 years.	42  Size 4.2 cm	73% at one year.	NR	Minimal discomfort.

SD: standard deviation

NR: Not reported

## **RECOMMENDATIONS OF OTHERS**

### **Blue Cross Blue Shield Association (BCBSA)**

The BCBSA Technology Evaluation Center has not conducted a review of this topic.

### **Centers for Medicare and Medicaid Services (CMS)**

CMS does not have a policy specific to the use of this technology.

### **American Society of Breast Surgeons (ASBS)**

An ASBS representative did participate at the meeting. The ASBS opinion regarding Management of Fibroadenomas of the Breast is available at: <http://www.breastsurgeons.org/fibro>.

### **American College of Surgeons, Northern California Chapter (ACSNC)**

The ACSNC did not comment regarding the use of this technology and did not attend the meeting.

### **American College of Obstetrics and Gynecology (ACOG)**

An ACOG representative was not able to attend the meeting and a formal opinion was not available for review.

## REFERENCES

1. Kaufman CS, Bachman B, Littrup PJ, et al. Office-based ultrasound-guided cryoablation of breast fibroadenomas. *Am J Surg*. Nov 2002;184(5):394-400.
2. Cant PJ, Madden MV, Coleman MG, Dent DM. Non-operative management of breast masses diagnosed as fibroadenoma. *Br J Surg*. Jun 1995;82(6):792-794.
3. Dixon JM, Dobie V, Lamb J, Walsh JS, Chetty U. Assessment of the acceptability of conservative management of fibroadenoma of the breast. *Br J Surg*. Feb 1996;83(2):264-265.
4. Greenberg R, Skornick Y, Kaplan O. Management of breast fibroadenomas. *J Gen Intern Med*. Sep 1998;13(9):640-645.
5. Carty NJ, Carter C, Rubin C, Ravichandran D, Royle GT, Taylor I. Management of fibroadenoma of the breast. *Ann R Coll Surg Engl*. Mar 1995;77(2):127-130.
6. Gordon PB, Gagnon FA, Lanzkowsky L. Solid breast masses diagnosed as fibroadenoma at fine-needle aspiration biopsy: acceptable rates of growth at long-term follow-up. *Radiology*. Oct 2003;229(1):233-238.
7. Hoffmann NE, Bischof JC. The cryobiology of cryosurgical injury. *Urology*. Aug 2002;60(2 Suppl 1):40-49.
8. Gage AA, Baust J. Mechanisms of tissue injury in cryosurgery. *Cryobiology*. Nov 1998;37(3):171-186.
9. Larson TR, Robertson DW, Corica A, Bostwick DG. In vivo interstitial temperature mapping of the human prostate during cryosurgery with correlation to histopathologic outcomes. *Urology*. Apr 2000;55(4):547-552.
10. Rui J, Tatsutani KN, Dahiya R, Rubinsky B. Effect of thermal variables on human breast cancer in cryosurgery. *Breast Cancer Res Treat*. Jan 1999;53(2):185-192.
11. Caleffi M, Filho DD, Borghetti K, et al. Cryoablation of benign breast tumors: evolution of technique and technology. *Breast*. Oct 2004;13(5):397-407.
12. Edwards MJ, Broadwater R, Tafta L, et al. Progressive adoption of cryoablative therapy for breast fibroadenoma in community practice. *Am J Surg*. Sep 2004;188(3):221-224.
13. Kaufman CS, Littrup PJ, Freeman-Gibb LA, et al. Office-based cryoablation of breast fibroadenomas with long-term follow-up. *Breast J*. Sep-Oct 2005;11(5):344-350.
14. Kaufman CS, Littrup PJ, Freeman-Gibb LA, et al. Office-based cryoablation of breast fibroadenomas: 12-month follow-up. *J Am Coll Surg*. Jun 2004;198(6):914-923.
15. Littrup PJ, Freeman-Gibb L, Andea A, et al. Cryotherapy for breast fibroadenomas. *Radiology*. Jan 2005;234(1):63-72.

16. Nurko J, Mabry CD, Whitworth P, et al. Interim results from the FibroAdenoma Cryoablation Treatment Registry. *Am J Surg*. Oct 2005;190(4):647-651; discussion 651-642.
17. Whitworth PW, Rewcastle JC. Cryoablation and cryolocalization in the management of breast disease. *J Surg Oncol*. Apr 1 2005;90(1):1-9.
18. Kaufman CS, Bachman B, Littrup PJ, et al. Cryoablation treatment of benign breast lesions with 12-month follow-up. *Am J Surg*. Oct 2004;188(4):340-348.
19. Simmons RM. Ablative techniques in the treatment of benign and malignant breast disease. *J Am Coll Surg*. Aug 2003;197(2):334-338.
20. Sperber F, Blank A, Metser U, Flusser G, Klausner JM, Lev-Chelouche D. Diagnosis and treatment of breast fibroadenomas by ultrasound-guided vacuum-assisted biopsy. *Arch Surg*. Jul 2003;138(7):796-800.
21. Takei H, Iino Y, Horiguchi J, et al. Natural history of fibroadenomas based on the correlation between size and patient age. *Jpn J Clin Oncol*. Jan 1999;29(1):8-10.
22. Markopoulos C, Kouskos E, Mantas D, et al. Fibroadenomas of the breast: is there any association with breast cancer? *Eur J Gynaecol Oncol*. 2004;25(4):495-497.
23. El-Wakeel H, Umpleby HC. Systematic review of fibroadenoma as a risk factor for breast cancer. *Breast*. Oct 2003;12(5):302-307.
24. Jacobs TW, Connolly JL, Schnitt SJ. Nonmalignant lesions in breast core needle biopsies: to excise or not to excise? *Am J Surg Pathol*. Sep 2002;26(9):1095-1110.
25. Houssami N, Cheung MN, Dixon JM. Fibroadenoma of the breast. *Med J Aust*. Feb 19 2001;174(4):185-188.