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

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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 (ACOSOG) 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.

INTRODUCTION

The trend in breast cancer treatment over the last several decades has been toward less invasive techniques. Breast-conserving surgery with radiation has been established as an oncologically sound alternative to mastectomy for the treatment of patients with unifocal, early-stage breast cancer. As systemic therapies have improved, the concept of decreasing the extent of local-regional therapies has been increasingly explored.

Building on significant experience in the treatment of benign breast tumors and metastatic hepatic tumors, the prospect of applying cryoablation therapy as a non-operative approach to breast cancer treatment has been considered worthy of investigation. Several investigators have shown the feasibility of cryoablation in the treatment of patients with small invasive breast cancers (IBCs), however most of these studies have been limited to single institutions enrolling small numbers of patients. As a result, many have questioned the applicability of cryoablation to the management of patients with breast cancer beyond the single institution setting where highly specialized centers have been established.

American College of Surgeons Oncology Group (ACOSOG) Z1072 was a phase II study evaluating the feasibility of cryoablation to treat early-stage breast cancer in a multicenter setting. The primary endpoint of Z1072 was the rate of complete tumor ablation, defined as no remaining IBC or ductal carcinoma in situ (DCIS) on pathological 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. The long-term goal would be to use cryoablation as an alternative to surgical resection in highly selected patients with early-stage breast cancers.

METHODS

Study Design

ACOSOG Z1072 was a phase II, non-randomized study evaluating the success of cryoablation in the treatment of breast cancer. The primary objective was to determine the rate of complete tumor ablation, with complete ablation defined as no remaining IBC or DCIS on pathologic examination of the targeted lesion. A secondary objective was to evaluate the negative predictive value of MRI in the post-ablation setting to determine residual DCIS or IBC. All eligible and registered patients underwent mammography, ultrasound, and breast MRI. Patients were treated with cryoablation followed by repeat breast MRI. A 1.5- or 3-Tesla magnet was used for all MRI images. MRI was evaluated by the institutional radiologist and by central radiology review.

Patients underwent surgical resection of the primary tumor within 28 days of the cryoablation. All patients had sentinel node biopsy or axillary dissection and adjuvant therapy as clinically indicated.

Patient Eligibility

Eligibility included unifocal invasive ductal carcinoma ≤2 cm, with <25 % intraductal component and tumor enhancement on MRI. Ninety-nine patients from 19 institutions were registered, and each signed an Institutional Review Board (IRB)-approved informed consent. Of the 99 patients, 86 were evaluable for the primary endpoint. One patient had bilateral disease and therefore outcomes are reported for 87 cancers. Thirteen patients were excluded for the following reasons: two had lobular histology, one had >25 % intraductal component, one had no tumor enhancement on MRI, and one had 1.0-Tesla MRI. Two patients did not have cryoablation, one did not undergo surgery, one was treated by a non-credentialed surgeon, one was treated prior to registration, one had a benign lesion, one withdrew consent prior to the start of the study, and one patient was not treated due to a probe failure.

Cryoablation Procedure

All cryoablations were performed using the commercially available Visica 2™ Treatment System. In accordance with US FDA market clearance, the Visica 2™ Treatment System was indicated for use in ablation of benign and malignant breast tumors. All patients were treated by a specific cryoablation algorithm, as outlined in the Z1072 protocol. MRI was performed 14–28 days after the cryoablation, and surgery was performed within 28 days after cryoablation.

Investigator Eligibility

Investigators were required to verify experience in cryoablation prior to enrolling patients, including documentation of a minimum of 20 interventional sonographically-guided procedures and a minimum of five sonographically-guided breast cryoablations.

Statistical Analysis

The primary objective of this study was to determine whether there was evidence that the complete ablation rate was above 90 % (indicating cryoablation is a potentially efficacious

treatment) or if there was evidence that it was <70 % (indicating current technology yields unsatisfactory results). The complete ablation rate was computed as the number of breasts with no residual disease after ablation divided by the number of eligible breasts. A one-sided 90 % binomial confidence interval (CI) was used to determine if there is evidence that the rate is ≥90 % or ≤70 %. A sample size of 90 breasts would have probability of 0.94 to yield evidence that the complete ablation rate is ≥70 % when the true rate is 90 %. In addition, a sample size of 90 breasts has 0.83 probability of yielding evidence that the complete ablation rate is <70 % when the true rate is 60 %. In addition to using the one-sided CI to determine the degree of evidence, the estimate of the complete ablation rate was provided by a binomial estimator and 90 % (two-sided) CI. The negative predictive value of MRI was estimated as the number of breasts with no residual disease after cryoablation and an MRI that indicated no residual disease, divided by the number of breasts with an MRI that indicated no residual disease. This was estimated with a binomial point estimate and corresponding 90 % binomial CI.

Categorical data are summarized as counts and relative frequencies, and comparisons among groups of interest were performed using the Fisher's exact test. Continuous variables were summarized as mean ± standard deviation (SD) and median (minimum value, maximum value). Comparisons between groups were made using a two-sample *t*-test. Analyses were carried out using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA). Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured through review by the Alliance Statistics and Data Center and the study chairperson following Alliance policies. Database lock date was 18 February 2014.

RESULTS

Baseline Characteristics

Eighty-six patients were included in the primary analysis dataset (Table 1). The first and last patients were registered on 16 March 2009 and 6 June 2013, respectively. Median age at registration was 62 years of age (range 42–81; mean ± SD 61.1 ± 9.3). One patient (1.2 %) had bilateral breast cancer. For all tumor measurements and outcomes, the patient with bilateral breast cancer was included; thus $N = 87$ breasts.

Magnetic Resonance Imaging (MRI) Results

All tumors showed pre-ablation enhancement on MRI, with enhancement characterized as a mass in 84 (96.6 %) breasts and non-mass-like enhancement in 3 (3.4 %) breasts. The mean ± SD tumor size on MRI was 1.2 ± 0.3 cm, and the median size was 1.2 cm (range 0.5–1.9 cm). Post-ablation residual enhancement was found in 23 (26.4 %) breasts (Fig. 1).

Surgical Procedures

All patients underwent surgical resection following cryoablation. Surgery was partial mastectomy in 85 (97.7 %) tumors, and mastectomy in 2 (2.3 %) tumors. Sentinel node biopsy was performed for 84 (96.6 %) tumors, and axillary dissection was performed for 10 (11.5 %) tumors (two at initial surgery and eight following positive sentinel node biopsy). One patient (1.1 %) did not have axillary assessment at the clinical discretion of the treating

surgeon. All patients received adjuvant therapy as clinically indicated by the treating clinicians.

Pathology Results

At surgical resection, all tissue was evaluated by the institutional pathologist and by central pathology review. On central pathology review, six patients were found to have benign disease that was originally interpreted as residual post-ablation IBC or DCIS by the institutional pathologist. The central review data were used in the final data analysis.

Primary Endpoint Analysis

Overall pathology results were analyzed without consideration of the location of the residual IBC or DCIS. Of the 87 cancers treated with cryoablation and eligible for evaluation, central pathologic review revealed successful cryoablation in 66 (75.9 %) cancers and residual IBC and/or DCIS in 21 (24.1 %) cancers. The 90 % CI for the estimate of successful cryoablation was 67.1–83.2 %, with the one-sided lower-sided 90 % CI of 69.0. Residual IBC (with or without residual DCIS) was found in 14 of 87 (16.1 %) breasts with a mean size (±SD) of 0.6 ± 0.6 cm and median size of 0.4 cm (range 0.05–1.9 cm). Residual DCIS alone was found in 15 of 87 (17.2 %) breasts with a mean size (±SD) of 0.6 ± 0.7 cm and median size of 0.3 cm (range 0.1–2.8 cm). Successful cryoablation, as determined by the institution pathology review, was observed in 60 breasts, corresponding to a success rate of 69.0 % (90 % CI 59.8–77.1)

Concordance of Post-Ablation MRI and Pathology

The negative predictive value of MRI was 81.2 % (90 % CI 71.4–88.8). A trend between MRI enhancement of residual tumor and the successful ablation was observed. There was 100 % ablation success in tumors that were radiographically <1.0 cm before cryotherapy without residual enhancement after cryotherapy, compared with 77.4 % success in those patients with tumors ≥1.0 cm and no residual enhancement (Table 2).

Pathology Results Relative to Cryoablation Zone

On central pathology review, the residual IBC and DCIS were categorized into four categories depending on the location of residual disease. Four categories were defined as ineffective (viable cancer in the cryoablation zone), incomplete (viable cancer at the edge of the cryoablation zone), misplaced (viable cancer away from the cryoablation zone and no evidence of necrotic cancer in the cryoablation zone), and multifocal (viable cancer in one or more foci >2.0 cm from the index tumor with necrotic cancer within the cryoablation zone). Four tumors were categorized as incomplete, two were categorized as misplaced, and 15 were categorized as multifocal (Fig. 2). Multifocal disease away from the targeted lesion was considered similar to residual disease surrounding the surgical site following breast-conservation therapy for the primary endpoint analysis. If this multifocal category is not defined as ablation failure, then 80 (92.0 %) of 87 cancers were successfully ablated, and 100 % of tumors <1 cm were successfully ablated (Table 3).

DISCUSSION

ACOSOG Z1072 was designed to evaluate the feasibility of cryoablation in the treatment of early-stage breast cancer in a multicenter setting. The primary endpoint was complete tumor ablation defined as no remaining cancer on pathologic examination of the targeted lesion. An overall successful ablation was observed in 66 of 87 (75.9 %; 90 % CI 67.1–83.2) cancers. When evaluating the targeted lesion, ablation was successful in 80 (92 %) of 87 cancers (multifocal disease outside of the targeted cryoablation zone was not defined as an ablation failure). The negative predictive value of MRI to determine residual IBC or DCIS was 81.2 % (90 % CI 71.4–88.8). These data suggest that modifications on the Z1072 protocol could be considered to evaluate the role for cryoablation as a non-surgical treatment of early-stage breast cancer, and that improved imaging is needed to detect multifocal disease outside of the targeted lesion. The clinical model for ablative therapy in breast diseases exists in the office-based practice of cryoablation for fibroadenomas. Cryoablation of fibroadenomas produces less pain and requires less anesthesia than surgical excision, and does not require removal of normal surrounding breast tissue. There is restoration of normal or near-normal breast architecture on examination and imaging. Some studies have shown complete clinical disappearance (physical examination, ultrasound and mammogram) of fibroadenomas within 1 year in 95 % of patients. [1,2]

The use of ablation technologies, including radiofrequency ablation, cryoablation, interstitial laser therapy, microwave thermotherapy, and focused ultrasound (FUS) ablation, are presently being explored to treat breast cancers as an alternative to surgical resection.[3–18] To replace surgical resection of breast tumors with cryoablation, complete tumor ablation must be performed with a high rate of success. To date, results of cryoablation for breast cancer have been highly successful, with complete cell death seen within the targeted ablation zone in the majority of cases. A pilot study of cryoablation in 27 patients with primary breast cancer documented complete ablation in those with infiltrating ductal carcinoma measuring <1 cm and in those with infiltrating ductal carcinoma ≤1.5 cm without an extensive intraductal component.[19] In one study, MRI has been shown to predict residual disease in a pilot study of radiofrequency ablation for breast cancer followed by surgical resection.[20] Previous studies have shown that residual foci of tumor commonly exist outside of the primary tumor site in patients treated with breast conservation. Some of these studies specifically looked at the incidence of foci of residual cancer on re-excision after initial pathology of IBC with negative margins and found the incidence of residual foci to be as high as 33 %.[21–22] Thus, it is not surprising we found foci of tumor in other areas of the breast outside of the targeted ablation zone in the Z1072 study. This was designated as a pathologic category of multifocal disease (viable cancer in one focus or multiple foci beyond the cryoablated zone with necrotic cancer in the cryoablation zone). These cases in Z1072 were re-evaluated and considered successful ablations for subsequent analysis. The success of cryoablation using this definition was 92 % in 80 of 87 cases. As with standard breast-conserving therapy, it is likely that radiation therapy would treat the subclinical foci outside of the targeted ablation zone without the need for additional surgical resection.

No cases were categorized as ineffective ablation (viable cancer within the cryoablation zone), which supports the effectiveness of the cryoablation technique. Any cases in this

category would imply a technical failure of the cryoablation process in forming a killing zone. There were four cases in the pathologic category of incomplete ablation (viable cancer at the edge of the cryoablation zone with necrotic cancer in the cryoablation zone), implying that the probe placement was effective to destroy some, but not all, of the targeted tumor. This may be an underestimate of tumor size by imaging or could imply an aberrant placement of the probe by the investigator. There were two cases in the pathologic category of misplaced ablation (viable cancer away from the cryoablation zone with no evidence of necrotic cancer in the cryoablation zone), implying aberrant placement of the probe by the investigator. The cases in the incomplete and misplaced categories are under further investigation to identify factors that could be improved in future trials.

CONCLUSIONS

In Z1072, cryoablation was effective in 92 % of targeted lesions and there was 100 % ablation in all tumors <1.0 cm. This supports the potential use of office-based, ultrasound-guided cryoablation in highly selected patients with IBC. The presence of multifocal disease may limit the efficacy of cryoablation as a stand-alone procedure and therefore it should be combined with adjuvant radiation. Further studies with modifications in technique and patient selection should be conducted to improve cryoablation success as a non-surgical alternative for breast cancer treatment.

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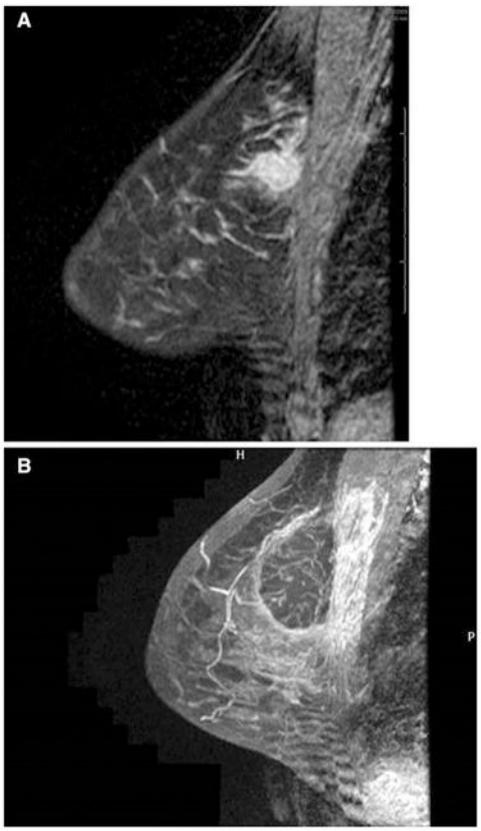

FIG. 1.

(**a**) Sagittal contrast-enhanced fat suppressed MR image of the breast before cryoablation demonstrates a 1.7 cm irregular mass with heterogeneous internal enhancement, representing the biopsy-proven carcinoma. (**b**) Sagittal partial maximum-intensity projection MR image of the breast obtained after cryoablation demonstrating the absence of the previously seen mass and a rim-enhancing structure or cryoball at the site of the carcinoma. Hyperemia or increased vascularity is noted around the cryoball. *MR* magnetic resonance

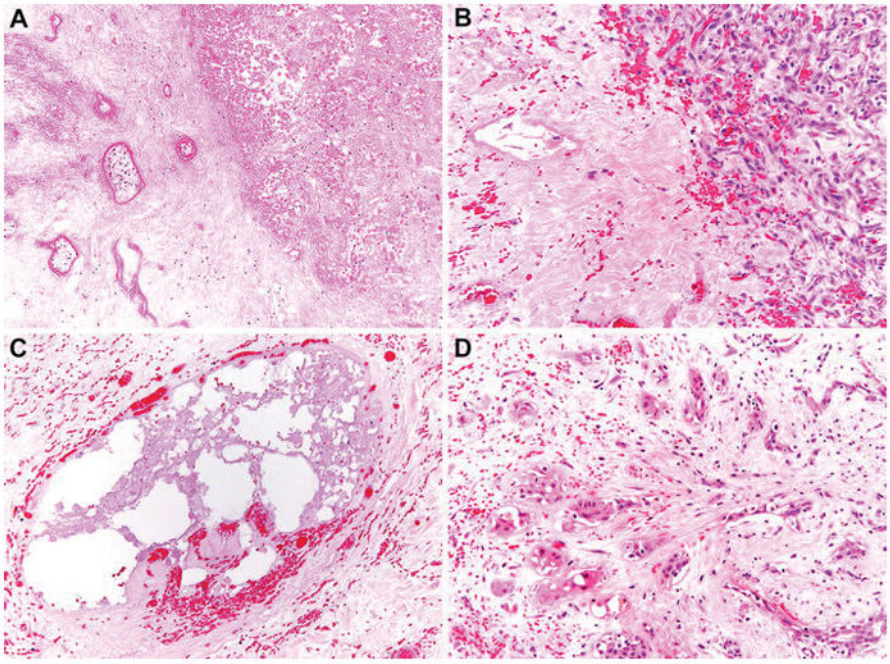

FIG. 2.

Variety of pathological changes seen status-post-cryoablation in malignant and benign tissues. (**a**) Histological appearance of completely necrotic tumor (*right*), status-post-cryoablation. No residual viable tumor is evident. Dilated necrotic blood vessels are present (*left*) amid edematous stroma. Note the lack of inflammatory cell reaction (H&E, ×20). (**b**) Granulation tissue, mainly characterized by proliferating capillary channels (*right*) adjacent to the necrotic zone (*left*) [H&E, ×60]. (**c**) 'Ghost' outline of neoplastic glands that have undergone coagulative necrosis (with loss of cellular viability, without architectural dissolution, leading to 'ghost' appearance) in the central portion of the cryoablated area (H&E, ×40). (**d**) Benign reactive squamous metaplasia in sclerosing adenosis at the perimeter of the cryoablated area (around the outer fibrosing zone). Such extent of squamous metaplasia in adenosis simulates invasive carcinoma. (H&E, ×60). *H&E* hematoxylin and eosin

TABLE 1

Patient and tumor characteristics

Patient characteristics (*n* = 86 patients)	
Age, years	
Median (range)	62.0 (42.0–81.0)
Mean ± SD	61.1 ± 9.3
Race	
White	71 (82.6)
Black	7 (8.1)
Asian	6 (7.0)
Not Specified	2
Ethnicity	
Hispanic/Latino	7 (8.9)
Non-Hispanic/Latino	72 (91.1)
Not specified	7
BMI	
Median (range)	27.1 (16.9–46.7)
Mean ± SD	27.9 ± 6.0
Unknown	1
Tumor characteristics [*n* = 87 breasts]	
Histology	
Infiltrating ductal	86 (98.9)
Other	1 (1.1)
Tumor grade	
Low	30 (38.0)
Intermediate	35 (44.3)
High	14 (17.7)
Unknown	8
Approximated tumor subtype	
HER2-positive	11 (12.6)
HER2-negative/HR-positive	75 (86.2)
Triple negative	1 (1.2)
Unknown	0
Tumor size by ultrasound, cm	
Median (range)	1.0 (0.0–2.0)
Mean ± SD	1.0 ± 0.4
Tumor size by mammography, cm	
Median (range)	1.1 (0.0–1.9)
Mean ± SD	1.1 ± 0.4
Calcifications	
Absent	22 (25.3)
Present	65 (74.7)

TABLE 2

Factors associated with successful ablation

	Successful ablation (*n* = 66)	**Unsuccessful ablation (*n* = 21)**	***p*-Value**
MRI status			0.050
Residual enhancement	14 (60.9)	9 (39.1)	
No residual enhancement	52 (78.8)	12 (18.8)	
HR status			0.99
Negative	3 (75.0)	1 (25.0)	
Positive	63 (75.9)	20 (24.1)	
Tumor grade			0.15
Low	26 (88.7)	4 (13.3)	
Intermediate	23 (65.7)	12 (34.3)	
High	10 (71.4)	4 (28.6)	
Tumor size, cm			0.10
<1.0	15 (93.8)	1 (6.3)	
≥1.0	51 (71.8)	20 (28.2)	
MRI status for tumor size <1.0			0.31
Residual enhancement	4 (80.0)	1 (20.0)	
No residual enhancement	11 (100.0)	0	
MRI status for tumor size ≥1.0			0.076
Residual enhancement	10 (55.6)	8 (44.4)	
No residual enhancement	41 (77.4)	12 (22.6)	
	Successful ablation or MRI residual disease	Unsuccessful ablation and MRI no residual disease	
Tumor size, cm			0.11
<1.0	16 (100.0)	0	
≥1.0	59 (78.7)	12 (21.3)	

TABLE 3

Factors associated with successful ablation (central review residual disease information)

	Successful ablation (*n* = 80)	**Unsuccessful ablation (*n* = 7)**	***p*-Value**
MRI status			0.37
Residual enhancement	20 (87.0)	3 (13.0)	
No residual enhancement	60 (93.8)	4 (6.2)	
HR status			0.99
Negative	4 (100.0)	0	
Positive	76 (91.6)	7 (8.4)	
Tumor grade			0.38
Low	29 (96.7)	1 (3.3)	
Intermediate	31 (88.6)	4 (11.4)	
High	12 (85.7)	2 (14.3)	
Tumor size, cm			0.34
<1.0	16 (100.0)	0	
≥1.0	64 (90.1)	7 (9.9)	
MRI status for tumor size <1.0			
Residual enhancement	5 (100.0)	0	
No residual enhancement	11 (100.0)	0	
MRI status for tumor size ≥1.0			0.36
Residual enhancement	15 (83.3)	3 (16.7)	
No residual enhancement	49 (92.4)	4 (7.6)	
	Successful ablation or MRI residual disease	Unsuccessful ablation and MRI no residual disease	
Tumor size, cm			0.99
<1.0	16 (100.0)	0	
≥1.0	67 (94.4)	4 (5.6)	