The eligibility of treating early cancer breast by US-guided radiofrequency ablation in Egyptian females

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Abstract

Introduction: This study was designed to determine the safety and efficacy of using percutaneous ultrasound-guided radiofrequency ablation of early breast carcinoma in Egyptian females.

Patients: Thirteen patients were included in the study to be treated just before scheduled mastectomy or breast conserving surgery.

Method: All patients were contraindicated or refused to do breast conservative surgery. A needle-shaped treatment electrode, with umbrella spreading end, was placed into the center of the lesions using ultrasound guidance. A temperature of 85ºC was maintained for 10 min. All resected specimens were processed & examined histopathologically using conventional methods searching for viable tumor cells.

Results: In 11 patients (84.6%), a complete ablation of the tumor was achieved. No extensive para-tumoural necrosis was detected in any case.

Conclusion: Ultrasound-guided radiofrequency ablation of breast carcinoma is feasible and safe. The success rate depends on accurate preoperative diagnostic imaging as well as the exact position of the needle electrode.

Key words: Radiofrequency ablation, pathological examination, cancer breast.

Introduction:

Breast cancer accounts for 25% of all cancers in women worldwide. The percentage reaches near one third of all carcinoma affecting Egyptian females. Although, incidence has been rising steadily over the last decades,[1-2] the mortality rate has remained virtually unchanged.[3] Today cancer treatment is multidisciplinary and there is an important general trend towards more selective interventions to minimize toxicity and late side effects without compromising efficacy. For example; sentinel node biopsy technique has, in many cases, replaced axillary lymph node clearance. Breast-conserving surgery in the form of wide local excision followed by breast irradiation is the appropriate therapy for early breast cancer, provided that the margins of resected specimens are free and that the excision can be performed with reasonable cosmetic result. Mastectomy is preferred in cases of extensive DCIS or large-sized cancer. Breast-conserving treatment has shown equivalent survival rates when compared to total mastectomy in large randomized studies.[4-5] During the past years several new methods for treatment of cancer breast have been investigated. These include cryosurgery, stereotactic excision, laser ablation, focused ultrasound and radiofrequency ablation.[6-7]

The main concerns and the remaining unsettled issues of these less invasive modalities of the treatment are the uncertainty of the extent (margin) of the lesion treated effectively and the viability of the tumor cells left potentially in the residual tissue afterward.[8]

Radiofrequency ablation is considered to be the most promising method due to its

constantly high success and low complication rates.[9] This is based on numerous feasibility studies showing complete ablation rates of 80-100%.[10-17] Furthermore an intrinsic property of this technique results in a preferential destruction of tumor cells with sparing of adjacent mammary tissue.[18] Considerable experience with this technique has already been acquired since it was previously demonstrated to effectively treat unresectable liver metastasis.[21] Furthermore, it has been shown in studies on small patient series that RFA can be performed in an outpatient setting under local anesthesia or blockade.[20-21]

Because of utilization of the intensive screening mammography, women's awareness of the disease, and our cosmesis-minded females, finding the small early breast cancer has become more of a reality than ever before. Therefore, these less invasive ablative procedures may have a chance to become a "standard procedure" for the local therapy of the early breast cancer if the oncological efficacy and safety is well established. Although radiofrequency ablation is an attractive approach as a local control method for small breast cancer, the problems of histological effectiveness and safety management remain.

The purpose of this study was to determine the efficacy and safety of percutaneous ultrasound-guided radiofrequency ablation (PRFA) of unifocal breast cancers with a radiological diameter of up to 30 mm.

Patients:

Thirteen patients aged between 37 and 69 years with tumor sizes of 16-30 mm where selected to receive PRFA treatment immediately before undergoing modified radical mastectomy or breast conserving surgery.

The current study was done between November 2010 to May 2011. The main inclusion criteria were presence of a unifocal tumor clearly distinguishable under US with a diameter of less than 30mm. None of the patients underwent preoperative chemo-or radiotherapy.

This study was approved by the Ethics Committee of Alexandria Faculty of Medicine, Egypt. If the patient fulfilled the inclusion criteria and was scheduled for radical mastectomy or breast conserving surgery, detailed information about the study was given and in case the patient agreed to participate a written informed consent was obtained.

A histopathological analysis of the tumor by core tissue biopsy was performed prior to surgery since the expected outcome of the study procedure was a destruction of the entire tumor. Histopathological examintion included: tumor type, grade, estrogen receptor, progesterone receptor and Her2.

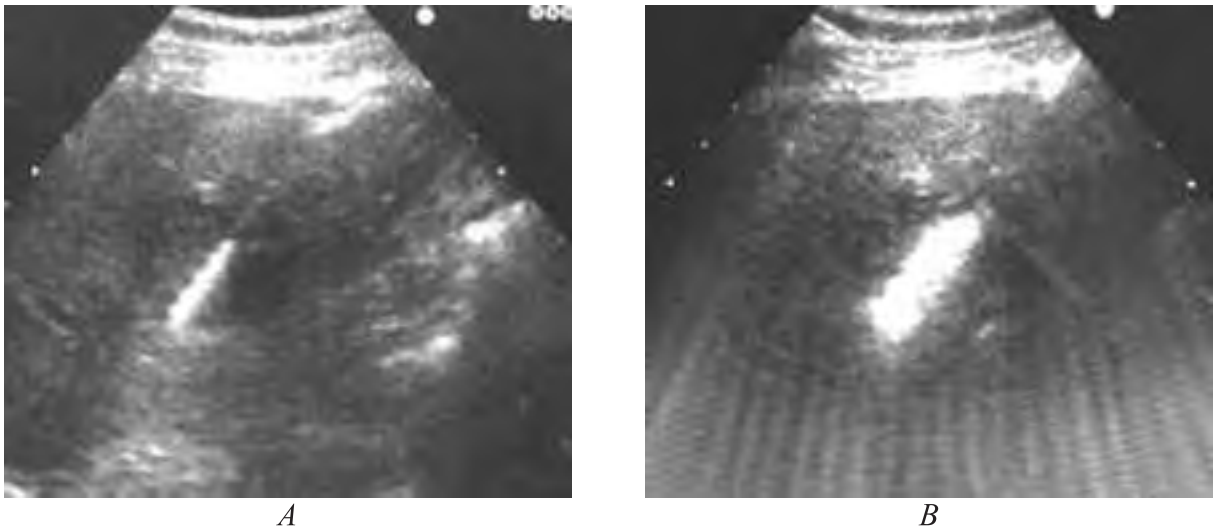
Method:

Ultrasound was used to identify tumor, needle introduction and to monitor treatment. The US instrument used was a Philips iU22 with a L5-17 linear broadband transducer (17-5 MHz frequency range). The specially designed RF-generator incorporated insulated cardiac-floating and low-impedance output subsystems. The electrodes used were of two different sizes. For the temperature measurement an integrated thermocouple, a specially designed low-pass filter and low level amplifier were used. The ablation procedures were performed by single experienced radiologists. In all cases, general anesthesia was induced and chest electrodes were attached to the back of the patient. The lesions were identified with ultrasound. Depending on the size of the tumor, a suitable needle electrode was selected and introduced into the lesion through a small incision under ultrasound guidance **Figure(1)**. With the goal to place the electrode in the center of the lesion, US images were taken in different projections. Thermoablation was then initiated by passing a successively regulated current between the needle electrode and the dispersive pad electrode. Tissue temperature was maintained at 70-85ºC for 10 min. Electrical impedance was monitored to improve thermal lesion control.

In order to protect the patient from burn effects to skin and underlying muscle special measures were taken. In ten cases several boli of local anesthesia (mepivacaine) with a nearly isotonic conductivity were injected to increase the distance between the tumor and the skin or pectoral muscle respectively to at least 1 cm.

Furthermore a sterile crushed ice pad was used for cooling. After treatment the tumors were resected according to scheduled procedure. The fresh specimens were subsequently sent to Pathology Departments for further evaluation.

The tissue was fixed in 4% buffered formalin solution and cut into 3-4 mm slices parallel to the electrode channel. The sheaves containing the necrotic lesion were easily identified and trimmed together with adjacent tissue, embedded and processed for large sections. The remaining tissue bordering the tumor area was cut at perpendicular angles to include the whole lesion and embedded in ordinary sized cassettes. The further processing followed established routines staining the cuts (4 μm) with H&E and according to van Gieson-elastin stain. Histopathological assessment was carried out by an experienced pathologist.



A *B*

Figure (1): Ultrasound of cancer breast before (A) & during (B) radiofrequency ablation.

Results:

For tumors with a size of up to 30 mm a treatment time of 10 min at 85ºC was judged suitable. Of the 15 patients enrolled at the beginning of this study two were excluded prior to treatment. In one case the tumor was too close to left sided chest wall with concerns about the usage of RFA on heart. In the other case the US-image prior to treatment was uncertain and the radiologist excluded the patient.

The average treatment time was 9±1.2 min with a range of 6-11 min. During treatment the target tissue became progressively echogenic under ultrasound to the point where the tumor margins could not be discerned any longer **Figure(1)**.

For the 11 (84.6%) of the 13 patients with complete ablation of the invasive component of the carcinoma, the tumors had a mean size of 21.7±3.2 mm (range 16.0-26.0 mm) whereas the created thermal lesion had a mean size of 35.9±3.1 mm (range 25.0-39.0 mm) according to final histopathological judgement. The difference in diameter between tumor and thermal lesion size was 9.2±4.2 with a range of 2.0-18.0 mm.

Table(1) shows data of the patients enrolled as well as radiologic and pathologic findings before treatment. The selected patients had a mean age of 53.2±7.8 years with a range of 36-69 years. In 86% of the cases the cancer was of ductal type. **Table(2)** shows a comparison of assessed tumor sizes using mammography and US.

Table (1): Demographics and diagnostic findings prior to treatment (n = 13).

Patient Age (years)		Menstrual status			Location of tumor		
Age	53.2±7.8	Premenopausal	2	(16%)	Left breast	5	(32%)
Range	36-69	Perimenopausal	1	(7%)	Right breast	8	(68%)
		Postmenopausal	10	(77%)			

Table (2): Comparison of assessed tumor sizes using mammography and US.

Mammo. tumor size [mm]		US tumor size [mm]	
Size	22±2.1	Size	24±1.6
Range	17-30	Range	16-30

Table (3): Patholgical findings of the tumors.

Histology			Grade		
Ductal	11	(86%)	I	3	(20%)
Lobular	1	(7%)	II	8	(67%)
Tubular	1	(7%)	III	2	(13%)

Table (4): Clinical data of patients and their management.

No.	Age	Axillary Lymph nodes	T. size Clin. [mm]	T. size US [mm]	RF Time [min]	Degree of ablation	Comments
1	36	No	10	8.5	10	yes	
2	52	No	9	9	9	yes	
3	69	No	10	7	10	yes	
4	46	No	n/a	10	7	yes	Treatment halted prematurely because of proximity to muscle
5	57	No	12	14	10	yes	
6	54	No	10	13	11	yes	Intraoperative detection and treatment of tumor extension
7	59	yes	12	8	10	no	Tumor extent larger than radiologically diagnosed, bifocal with an extra lesion of 11 mm
8	56	No	10	10	7	no	Treatment halted prematurely because of significant swelling
9	57	yes	10	14	7	yes	Treatment time reduced due to location of the tumor
10	61	No	15	15	7	yes	Treatment time reduced due to location of the tumor
11	67	No	15	15	11	yes	
12	54	No	14	14	10	yes	
13	58	No	13	13	10	yes	

Histologic changes:

There was a well-established early complete coagulation necrosis. The changes were evident in all tissue elements including epithelium, connective tissue and fat tissue. The regressive changes could also be followed in the fibro-tumorous extensions from the main tumor mass and to a lesser extent in adjacent fat tissue **Figure(2)**. In the epithelium, there was nuclear condensation or loss of nuclear details, homogenisation of the cytoplasm and accentuation or loss of the cellular membranes. The connective tissue showed homogenisation, loss of nuclei and loss of the normal birefringence, most evident in the van Gieson stain. The fat tissue adjacent to the fibrous tissue only showed a thin well-delimited rim, approximately 1 mm, of slight vacuolar degeneration and preserved nuclei.

In contrast, the lobular carcinomas with their irregular outline and diffuse shape showed an even circular shape of necrosis around the electrode canal.

In all instances, the borderline between tissue with thermally induced degeneration and normal appearance did not exceed a couple of millimeters judged by routine microscopy.

To further understand the effects of PRFA on breast carcinoma, a small section was removed on the border of tumor tissue and surrounding fat tissue using H&E staining. Scanning with electron microscope (SEM) shows a clear difference between ablated and non-ablated tissue as well as a remarkably sharp line of demarcation can be seen.

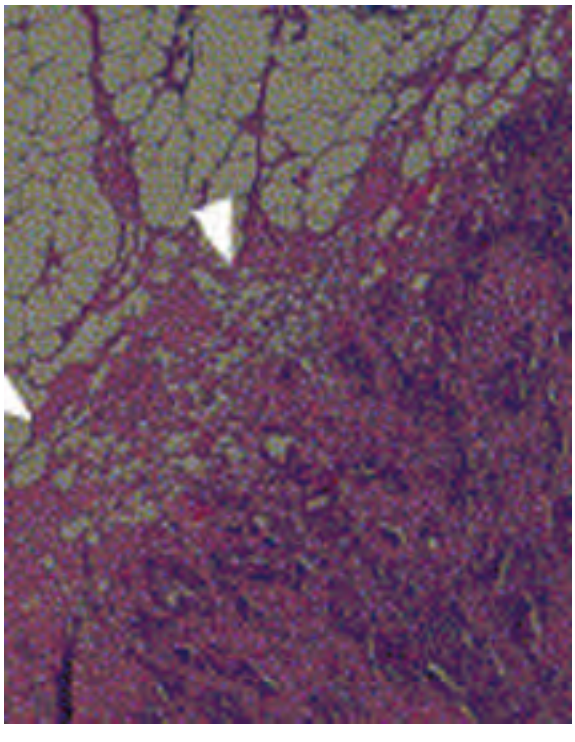


Figure (2): Denaturated ductal carcinoma and adjacent preserved fat. H&E.

Discussion:

Radiofrequency ablation is a lean method of destroying tumors on an outpatient basis. For the treatment procedure, a dispersive pad electrode is attached to the patient and a needle electrode is inserted into the tumor under US guidance. When an RF current is passed between the electrodes ion agitation causes friction and thus a temperature rise in proximity of the needle electrode where current density is highest.

An inherent property of radiofrequency ablation applied to breast malignancies is the preferential heating of tumor tissue, while fatty tissue is left relatively unharmed. This was shown in both in-vitro studies as well as finite element method (FEM) simulations.[17-18] The explanation for this is differences in electrical and thermal parameters between the tissue types. However, the observed preferential heating in the in-vivo as well as in-vitro studies were more pronounced, indicating that

additional effects other than the difference in tissue parameters might be involved.

During the last decade, several studies have been performed using different study designs[9-16] combining immediate, delayed or excluding surgery as well as applying different treatment electrodes and patient inclusion criteria. Success rates were generally high with only minor complications and excellent cosmetics. Incomplete tumor ablation was often explained by improper insertion of the needle electrode, too short distance to skin/pectoralis and an underestimation of tumor extent preoperatively.

It has been stated that to correctly assess the effects of radiofrequency ablation, NADH-diaphorase is more suited, since H&E often underestimates the lesion size. Judging that measurement of radicality and lesion size were of primary importance to the study which demands immediate fixation and inking excluding enzymatic stain as well as following hospital protocols we decided to use classical morphology with H&E staining. Due to the short time interval between PRFA and surgery, the zone of ablation in this study is probably underestimated as there was no time for the injured tissue to develop the spectrum of degenerative changes seen in longer time intervals. The therapy response was therefore graded in either necrotic or non-necrotic. The observed borderline between viable and regressive areas furthermore had a magnitude of millimeters and there is no adverse effect for the study with regards for this possible underestimation of the size of the ablation. The SEM findings indicate an even more abrupt transitional zone.

Lobular cancer was not an exclusion criterium in this study. Two cases were accepted due to the fact that one important circumstance in this study situation was that all primary cancers were to be subsequently removed by surgical excision. In agreement with other authors, we find that lobular cancers have properties that are unfavorable for PRFA treatment.

Our study confirmed the need for a safety distance between the tumor and the skin by using active cooling or by infusion of a bolus volume such as mepivacaine to increase the distance and maintain similar electric impedance. However, there are limitations of the possibility to manipulate tumor location in this way. We observed that injected liquid volumes diffuse into the surrounding fat tissue. This could be visualized as the procedure was followed by US. In addition, we used traction sutures to manually increase the distance between lesion and thoracic wall and skin respectively.

This study also confirmed that one drawback for this method is the difficulty to deploy the needle in a suitable position in the center of the tumor. A possible way to tackle this is to use 3D ultrasound to determine the position of the needle electrode as was previously shown to be effective for hepatic malignancies.[25] A further idea to facilitate the insertion especially when dealing with hard tumors, is to add a mechanical vibration. A longitudinal sinusoidal movement of the needle would significantly reduce friction and thus decrease insertion force.

The other main drawback of this method is the inability to validate ablation margins without surgical resection as well as the pretreatment detection of extensive intraductal components. This problem could be reduced by including MRI into the treatment protocol.

Conclusion:

The outcome of our study confirms the potential of PRFA for the treatment of small breast cancer in Egyptian females. It offers a high success rate, a low rate of minor complications as well as good cosmetics. Compared to current treatment protocols, this method is far less traumatic, making it possible to provide local tumor control for previously untreatable patients in weak and unstable condition. Several publications report PRFA treatments performed in an outpatient setting under local anesthesia. By treating breast cancer in an outpatient setting, the need for an operating room setup is avoided, thereby possibly creating economic advantages. Another aspect of this technique is the potential as an adjuvant measure to invasive surgery. PRFA treatment could be performed immediately following pretreatment diagnosis, thus halting further tumor progression. Of course, local hospital protocols have to be

taken into consideration. In conclusion, PRFA promises to be a safe, feasible and patient-friendly method of treating small unifocal breast adenocarcinoma. If our results are confirmed by larger clinical trials in future, then PRFA would eliminate open surgery and decrease the morbidity associated with lumpectomy and radiation.

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