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Original article

Ultrasound-guided radiofrequency ablation of early breast cancer in a resection specimen: Lessons for further research

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ABSTRACT

Purpose: To assess the feasibility and effectiveness of radiofrequency ablation (RFA) in breast cancer, using different histopathologic staining methods to evaluate tissue viability.
Materials and methods: In twenty patients with unifocal small (≤1, 5 cm) invasive ductal carcinoma, ultrasound-guided RFA was performed immediately after surgery. Cell viability was assessed using cytokeratin 8 (CK 8) and nicotinamide adenine dinucleotide diaphorase (NADHD) in addition to hematoxylin–eosin (HE).
Results: At histopathological examination, ex vivo RFA resulted in complete cell death of the target lesion in 17/20 patients. In two cases viable ductal carcinoma in situ (DCIS) was found just outside the completely ablated lesion.
Conclusion: RFA of small invasive breast cancer seems to be a feasible treatment option. Both NADHD and CK 8 demonstrate a clear and comparable demarcation between viable and non-viable tissue. A high level of accuracy is required in proper positioning of the needle electrode and a "hot retraction" is mandatory.

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Introduction

During the last few decades there has been a trend toward less aggressive local treatment of breast cancer, which has led to the widespread use of breast conserving surgery and the introduction of the sentinel node biopsy.[1,2] Percutaneous minimally invasive techniques to locally eradicate tumors are studied in order to further improve the impact of treatment and reduce side effects, such as cryoablation,[3] laser ablation,[4] high-intensity focused ultrasound (HIFU)[5] and radiofrequency ablation (RFA).[6–25]

RFA is a technique based on the principle of tissue electro coagulation[26] after placing a needle-electrode in the center of a tumor. During ablation a high-frequency alternating current flows through the surrounding tissue. As ions try to follow the current, they cause heat due to friction. Not the electrode, but the surrounding tissue is the source of heat. The heat transfers conductively to more distant tissue, creating an ellipsoid region of necrotic tissue aligned with the needle-electrode tip.

Recent published studies investigating RFA in breast cancer show a high complete response rate and just minor complications, i.e. skin burns and wound infections in a minority of patients. Until now, less attention has been paid to different methods to assess cell viability. We performed an ex vivo study to determine the feasibility of this promising technique in our clinic as a precursor to an in vivo study, in which we will ablate the tumor, followed by immediate resection. We evaluated post-RFA cell viability using different histopathologic staining methods, i.e. cytokeratin 8 (CK8) as well as nicotinamide adenine dinucleotide diaphorase (NADHD). NADHD is currently considered to be the gold standard, but it requires frozen material, which is associated with poor morphology.

Materials and methods

Postmenopausal patients with a unifocal small (≤1.5 cm) breast cancer lesion were considered eligible for this institutional review board (IRB) approved study. Only patients with invasive ductal carcinoma were included. Furthermore, tumor characteristics such as Bloom Richardson grade, estrogen- and progesterone receptor

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status, and *HER-2*/neu status were determined at the core needle biopsy, to ensure optimal treatment.

Patients with the histopathological diagnosis of carcinoma in situ or lobular carcinoma, insufficient visualization of the tumor by ultrasound (US), multiple tumors in the same breast and previous surgery or radiotherapy of the breast were excluded.

The radiofrequency ablation was performed using the Cool-tip RF ablation system (Tyco Healthcare Nederland BV, Zaltbommel, The Netherlands). This system consists of a 17 gauge straight electrode, which circulates water internally to cool the tissue adjacent to the electrode, maximizing energy deposition and reducing tissue charring. The electrode used ablates an area with a diameter of 2 cm. The 200 Watt generator delivers 480 kHz pulsed energy to the surrounding tissue. The system's generator feedback algorithm senses tissue impedance and automatically delivers the optimum amount of radiofrequency energy. Treatments are typically completed in 12 min.

After lumpectomy or mastectomy, the specimen was placed on top of a grounding pad. RFA was performed by one of two radiologists (MR, GJ), who both have extensive experience in both breast US and radiofrequency ablation of liver tumors. After localization of the tumor by US, the needle-electrode was placed in the center of the tumor. The position of the needle was verified in different directions. The generator was switched on and RFA was performed for 12 min. This process was monitored using US at random intervals of a few minutes. After the procedure the temperature of the ablated tissue was determined using the thermocouple at the tip of the needle-electrode.

Following ablation whole mount sectioning was performed of the specimen. At the level of the tumor, the specimen was divided into two equal parts (mirror images): one part was formalin fixed, the other part was snap frozen and stored at −80 °C. Formalin fixed tissue was used for routine histopathological evaluation using conventional hematoxylin–eosin (H&E) staining. For immunohistochemical staining, 3 μm parallel paraffin embedded sections were routinely stained with a monoclonal antibody to cytokeratin (CK) 8 (CAM5.2, Becton & Dickinson, Erembodegem-Aalst, Belgium). Stainings were developed in 3-3′-diaminobenzidine tetrachloride (DAB) after application of the peroxidase LSAB kit (Dako Cytomation, Glostrup, Denmark). Finally, sections were counterstained with Mayer's hematoxylin. For enzyme histochemistry, 8 μm frozen sections were incubated by a mixture of reduced α-NADH (Sigma–Aldrich, Zwijndrecht, The Netherlands), nitroblue tetrazolium chloride (Sigma–Aldrich), ample phosphate-buffered saline and Ringers solution (Baxter, Utrecht, The Netherlands). Subsequently sections were mounted using Aquatex mount medium (Merck, Darmstadt, Germany).

For both CK8 and NADHD untreated liver tissue was used as a positive control and RFA-ablated liver tissue as a negative control. Pathologic evaluation of the sections was performed to assess the effects of RFA and cell viability.

Results

Twenty postmenopausal women with a mean age of 66 years (range 51–78 years) were included after signing informed consent. Preoperative diagnostic imaging showed an average tumor diameter of 9.8 mm (range 4–15 mm). Seventeen of twenty invasive ductal carcinomas were estrogen receptor positive and twelve were progesterone receptor positive as well, as determined by core needle biopsy. Bloom Richardson grade was 1 in ten lesions and 2 in the remaining ten. Only one tumor was HER-2/*neu* positive.

Fourteen patients had a lumpectomy and six underwent a mastectomy. In all cases the RFA procedure was technically successful. The impedance at the beginning of the ablation ranged from 70 to 180 Ohm (mean 113 Ohm ± 30 SD). At the end of the procedure the mean temperature was 55 °C (range 40–90 °C). The RFA process was monitored with ultrasound, but the visibility of the target lesion decreased in all cases due to development of an ill-defined hyperechoic zone around the tip of the needle electrode (Fig. 1) (Fig. 2).

Mean tumor size at histopathological examination was 12 mm (range 7–23 mm) and the diameter of the ablated area ranged from 13 to 40 mm (mean 27 ± 7 mm). In all cases a thermal effect was seen when examining the hematoxylin and eosin stain. A clear and comparable demarcation between viable and non-viable tissue was demonstrated by both NADH diaphorase and cytokeratin 8 immunostaining (Figs. 3 and 4). In 17 patients RFA had resulted in

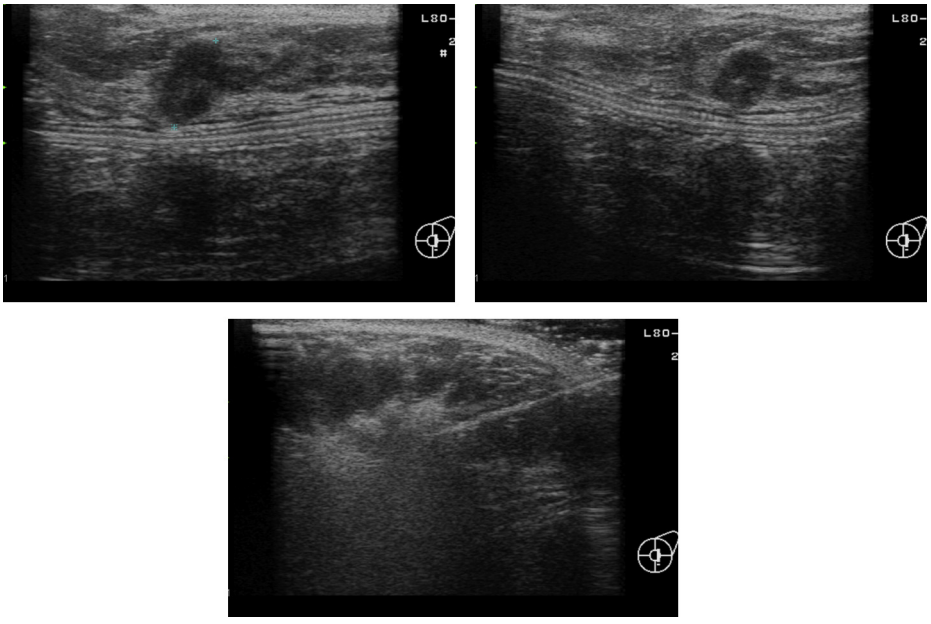

Fig. 1. Ultrasound images showing, visualization of the tumor (upper left), needle electrode placement (upper right) and RFA of the tumor (lower image).

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