The Breast 23 (2014) 152–158

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Minimally-invasive treatment of early stage breast cancer: A feasibility study using radiofrequency ablation under local anesthesia☆

Kai-Uwe Schässburger [a,*], Lars Löfgren [b], Ulla Lagerstedt [g], Karin Leifland [c], Karin Thorneman [c], Bengt Sandstedt [d], Gert Auer [e], Hans Wiksell [f]

[a] Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Solna (L1:00), 17176 Stockholm, Sweden
[b] Department of Surgery, Capio S:t Görans Hospital, 11281 Stockholm, Sweden
[c] Department of Mammography, Unilabs AB, Capio S:t Görans Hospital, 11281 Stockholm, Sweden
[d] Department of Pathology, Karolinska Universitetslaboratoriet, Karolinska Institutet Danderyds Sjukhus, 18288 Stockholm, Sweden
[e] Department of Oncology-Pathology, Karolinska Institutet, Karolinska University Hospital, (Z5:02), 17176 Stockholm, Sweden
[f] Department of Molecular Medicine and Surgery, Karolinska Institutet, P.O. Box: 39011, 10054 Stockholm, Sweden
[g] Department of Pathology, Unilabs AB, Capio S:t Görans Hospital, 11281 Stockholm, Sweden

ARTICLE INFO

Article history:
Received 9 August 2013
Received in revised form
30 October 2013
Accepted 7 December 2013

Keywords:
Breast cancer
Minimally invasive
Radiofrequency ablation
Small breast carcinoma

ABSTRACT

The objective of this study was to assess efficacy and safety of percutaneous ultrasound (US) guided preferential radiofrequency ablation (PRFA) in early breast carcinoma under local anesthesia and to evaluate a new assessment protocol. Eighteen breast cancer patients were enrolled in order to receive PRFA treatment three weeks prior to resection. Pain assessment was performed using the visual analoge scale. Analysis of treatment success was performed using magnetic resonance imaging (MRI) as well as histological assays for hematoxylin & eosin (H&E) and cytokeratine 8 (CK8). In a subset of patients contrast enhanced ultrasound (CEUS) was performed before and after treatment. MRI showed no residual tumor growth in 100% (18/18) of cases. Complete tumor devitalization was indicated in 83% (15/18) of patients as judged by H&E staining and in 89% (16/18) as judged by immunostaining for CK8. In 100% (18/18) at least one histologic method showed devitalization in the entire tumor. Treatment was well tolerated. Pain experienced during the procedure was mild. US-guided PRFA of small breast carcinoma is feasible under local anesthesia. MRI and CK8 have proven valuable additions to the RF breast tumor ablation protocol. CEUS shows potential as a modality for radiological follow-up.

Introduction

Globally an estimated 1.64 million women were diagnosed with breast cancer in 2010 with incidence increasing most markedly in developing countries resulting from a change in lifestyle conditions, reproductive patterns, increasing average age and use of hormone replacement. While mortality is comparatively high in developing countries it remains constant or is falling in developed countries due to advances in medication and radiotherapy as well as tumor detection in earlier stages as a result of screening programs. In Sweden, which was one of the first countries to implement a national screening program in 1986, the median tumor size in breast cancer patients diagnosed 2011 was 17 mm. There is a general trend towards less invasive treatment regimes. Lumpectomy followed by radiation therapy is the preferred surgical treatment in women with unifocal breast cancer if the procedure is expected to yield a cosmetically acceptable result. Sentinel lymph node biopsy has replaced axillary node clearance as the gold standard for staging of the axilla. In the wake of this development, minimally-invasive technologies for breast cancer treatment have been studied using several different approaches. Radiofrequency ablation (RFA) seems to be the most promising technology given its constantly high success rates, short treatment time, low complication rates [1] and preferential destruction of tumor tissue as compared to surrounding fatty tissue [2].

However, several issues remain to be addressed before the modality can expect widespread acceptance. Histological assessment of RF treatment success is problematic. Standard H&E staining proves unreliable when assessing RF treatment success [3], generally underestimating RF damage when performed shortly after treatment [4,5]. Mammography and US are unsuitable to radiologically evaluate treatment outcome [6,7]. Futhermore, while there is ample data on treatment under general anesthesia, experience is limited concerning treatment under local anesthesia in an

* Corresponding author. Department of Molecular Medicine and Surgery, Karolinska Institutet, NeoDynamics AB, Lejonvägen 14, 181 32 Lidingö, Sweden. Tel.: +46 (0)762 386 153.
E-mail address: kai-uwe.schassburger@ki.se (K.-U. Schässburger).

0960-9776/$ – see front matter © 2013 The Authors. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.breast.2013.12.007

outpatient setting. Finally, although precision placement of the electrode is crucial [8] there are currently no means available to facilitate the cumbersome process of manual large diameter electrode placement. Based on initial institutional experience in the use of PRFA in breast cancer patients [2,9] the goal of this study was to move the treatment into an outpatient setting and tackle the identified shortcomings. The radiological protocol for patient selection and treatment follow-up was improved by including MRI and CEUS. Histological assessment was performed using CK8 immunohistochemistry as well as H&E and means for power-assisted precision placement were introduced to aid the placement of the treatment electrode.

Materials and methods

Patients

Patients included in our study had to be diagnosed with a unifocal, clearly distinguishable tumor with a maximum diameter of 16 mm as assessed by mammography, US and MRI. Exclusion criteria included multifocality, diffuse growth patterns, tumors with surrounding ductal carcinoma in situ (DCIS) and lobular cancer. In line with ongoing clinical trials on minimally-invasive ablation technologies at the time (e.g. trial NCT00723294) the inclusion criteria were altered during the course of the study to enable the inclusion of patients with tumors that were ER/PR negative, Her2/neu positive, of Elston grade 3, had a size of $\leq$2 cm and showed $\leq$25% of intraductal components. The study was approved by the Regional Ethics Committee of Stockholm, Sweden (Ref. nr. 2008/1018-31/3; 2010/963-32) and all procedures were performed in accordance with the ethical standards of the World Medical Association (Declaration of Helsinki). If the patient fulfilled the inclusion criteria, detailed written information about the study was given. If the patient agreed, a written consent was obtained. Core biopsy samples prior to PRFA treatment were retrieved and analyzed regarding histological type, Elston grade and receptor status (estrogen receptor, progesterone receptor, Her2/neu, Ki67 and CK8).

RF treatment instrumentation

Radio frequency heating can be utilized to act preferentially in breast cancer tumors, heating tumor strands relatively more than surrounding non-tumor tissue [2]. It is therefore named preferential radiofrequency ablation (PRFA). Successively developed prototypes (NeoDynamics AB, Sweden) incorporating an internally cooled electrode design were used. The instrumentation is approved by the Medical Products Agency, Uppsala, Sweden (Ref. code 561:2010/503820) for the purpose of this study and conforms to the international safety norm EN 60601-1. In a previous study at our institution it was reported that the insertion procedure of the needle was problematic in certain cases due to a hard consistency of the tumor in comparison to the surrounding soft fatty tissue [9]. Since correct placement of the treatment electrode is crucial for optimal treatment, a handheld driver unit for power-assisted insertion of the electrode as well as a specially designed treatment electrode was developed. The driver unit aids the operator by delivering triggered mechanical pulses thrusting the needle forward over a controlled millimeter distance when encountering hard to penetrate tissue.

Imaging modalities

For MR imaging a 1.5 T (Signa HDxt, GE Healthcare, USA) system was used in combination with an intravenous gadolinium contrast agent (ProHance, Bracco Diagnostics, Italy). Ultrasonographic (US) imaging was performed with an iU22 ultrasound device (Philips, Netherlands) together with transducer L17-5 (17-5 MHz frequency range) for common US and L9-3 (9–3 MHz frequency range) for contrast-enhanced ultrasound (CEUS). The latter involved an intravenous administration of sulfur hexafluoride microbubbles with a size of 1–10 μm (Sonovue, Bracco Diagnostics, Italy).

Treatment protocol

The first four cases were treated in the operating theatre at the department of surgery. Treatment was performed under local anesthesia with means for administration of additional sedation/analgesia available. In the inpatient setting patients routinely received 1 g paracetamol and 25 mg meclozine before thermal ablation. Upon discharge patients received 5 mg oxycodone and 500 mg paracetamol according to routine department protocol. Subsequent 14 patients were treated in an outpatient setting at the department of mammography. 40–75 ml of mepivacaine (5 mg/ml) and bupivacaine (2.5 mg/ml) combined with 5 μg/ml epinephrine were injected at the insertion site as well as adjacent to the tumor for pain control and to alienate the tumor from the skin and pectoral muscle. Tissue temperature was kept at 85 °C for 10 min. Electrical impedance was monitored in order to improve thermal lesion control. To avoid thermal damage skin temperature was monitored using a handheld 650 nm laser guided IR thermometer. Ice was used for cooling. As suggested by several authors [8,9], the electrode was routinely active upon retraction in order to prevent possible seeding of disseminated tumor cells.

Pain assessment protocol

In order to quantify perceived pain resulting from PRFA treatment under local anesthesia a measurement was performed using the visual analoge scale (VAS, from 0 to 10; 0 = no pain, 10 = unbearable pain). Since the VAS is less useful for comparative analysis across a group of individuals at one time point, but more suitable for comparing events in a single individual, pain assessment was performed at four different stages during the procedure. The patient was specifically asked to judge pain before treatment, during administering of local anesthetics, during PRFA treatment and after completion of the procedure. Furthermore, if there was any discomfort whatsoever between the time of PRFA treatment and surgery, it was noted.

Radiological and histological assessment

MRI was performed before and after PRFA treatment close to the date of surgery. In a subset of six patients CEUS was performed before and after PRFA treatment. PRFA treatment was carried out by an experienced radiologist. Resected specimens underwent radiography to evaluate extent and surgical margins. Subsequently specimens were fixed in 4% buffered formalin and cut into 3–4 mm slices. Sheaves containing the necrotic lesion were identified, trimmed, paraffin embedded and processed into 4 μm sections. For histopathological evaluation using H&E the sections were stained following validated standard hospital protocol. For immunohistochemical staining paraffin embedded sections were stained with a monoclonal antibody to CK8 (35betaH11, Ventana Medical Systems, Inc., Tucson, USA) using validated hospital standard protocol. A tris-based buffer with a slightly basic pH (Cell Conditioning 1, Ventana Medical Systems, Inc.) was used for pre-treatment. Sections were subsequently counterstained with Hematoxylin II as well as Bluing Reagent (Ventana Medical Systems, Inc.) and finally fixated and mounted. An automated Benchmark XT (Ventana Medical Systems,