Long-term outcome of breast cancer patients treated with radiofrequency ablation

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Abstract

Background: Radiofrequency ablation (RFA) is considered to be the most promising non-surgical ablation technique for the treatment of small breast cancer. However, few data are available regarding long-term follow-up of patients treated with this modality.

Methods: Since 2005, we have performed RFA and sentinel lymph node (SLN) biopsy in 19 cases. Axillary lymph node dissection (ALND) was performed in patients with positive SLNs. From 24 to 202 days after RFA, the ablated tumour tissue was excised by mammotome biopsy and examined histologically or immunohistochemically with H&E staining, nicotinamide adenine dinucleotide (NADH)-diaphorase staining, and single-stranded (ss) DNA staining. All cases were followed-up after breast radiation and systemic therapies.

Results: Although complete response was histologically confirmed in only 8 cases, NADH-diaphorase and ssDNA staining did not demonstrate any viable tumour cells in the ablated lesions. At a mean follow-up of 60 months (follow-up range, 37–82 months), there were no cases of in-breast recurrence, although one patient died due to hepatic metastases. Cosmesis of the conserved breast was excellent or good in all of the cases, but a hard lump was persistent after RFA in half of the cases.

Conclusions: The long-term outcome of patients treated with RFA is encouraging with regard to cosmesis and local control. Because a persistent lump may cause patient discomfort, anxiety and fear, however, further studies are needed to establish the optimal technique. Moreover, a prospective study will be required to determine the equivalency in local recurrence rates between the RFA therapy and conventional breast-conserving treatment.

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Introduction

Currently, breast-conserving treatment (BCT) combined with partial mastectomy and breast irradiation is widely accepted as the standard form of treatment for early breast cancer. The aims of BCT are to achieve local control and survival rates equivalent to total mastectomy, while preserving the appearance of the breast. This treatment has great cosmetic advantages over total mastectomy. However, cosmetic failure is more common than generally realized, occurring in up to half of all patients after BCT.1–5 This is most closely linked to volume loss of breast tissue, leading to retraction, asymmetry, and to scarring, due to inappropriate incisions and radiotherapy.1,6 With the widespread implementation of mammography screening programs and increasing awareness among women, breast cancer is detected earlier while the lesions are still small, which facilitates easier treatment with minimally invasive approaches. There is increasing demand for minimally invasive and non-surgical treatment for patients with small breast cancer.

So-called minimally invasive techniques have been developed to treat primary breast cancer, leading to BCT without surgery. This type of BCT does not require a breast skin incision and does not remove large volumes of breast tissue, thereby resulting in improved breast cosmesis. Among various methods of minimally invasive therapy, radiofrequency ablation (RFA) therapy is considered the most promising method due to its consistently high success rates.
and low complication rates.\textup{7--10} In feasibility studies, the ablated tumour was surgically removed after RFA, and the tumour cell viability were assessed by histological and/or immunohistological examinations.\textup{11--26} However, these assessments of tumour viability do not take the place of long-term follow-up in patients treated with RFA alone, because they do not allow for them to be followed up for recurrence after RFA, or to determine if there were any undesirable complications of this procedure.\textup{27} Therefore, the adequacy of RFA therapy can be determined only when the results of long-term follow-up of patients treated with this modality are available.\textup{10} Here, we report the oncological and cosmetic long-term outcomes in patients undergoing this procedure followed by mammotome excision.

Patients and methods

Patients

Between October 2005 and April 2009, 18 patients with histologically proven invasive breast cancer less than 2.0 cm in greatest diameter and without clinically axillary involvement (T1N0M0) were enrolled in this study. Breast tumours were confirmed to be localized lesions by mammography, ultrasonography (US), magnetic resonance imaging (MRI), and/or enhanced computed tomography (CT). Exclusion criteria included patients with multifocal or multicentric breast cancer and breast cancer with intra-ductal spreading diagnosed with these modalities. Patient with bilateral breast cancer was included. None of the patients underwent primary chemotherapy. The diagnosis of breast carcinoma was established based on histological examination with hematoxylin & eosin (H&E) staining using tumour specimens obtained by US-guided core needle biopsy. The hormone receptor status and HER2/neu status were also examined by immunohistochemical analysis of these specimens. All enrolled patients provided written informed consent as approved by the Clinical Investigation and Ethics Committees of Yatsuo General Hospital.

RFA procedure and SLN biopsy

US-guided RFA with sentinel lymph node (SLN) biopsy was performed under general anesthesia. The dye-guided method and CT-lymphography were used to identify SLNs.\textup{18} The identified SLNs were removed and frozen sections were examined histologically during surgery. The method of RFA therapy has been described in detail elsewhere.\textup{12,18} After SLN biopsy, a primary electrode (seven-array model 70 Starburst needle electrode; RITA Medical Systems, Mountain View, CA) (Fig. 1a) was inserted into the tumour under real-time US guidance (Hitachi EUB-6000 digital ultrasound scanner system; Hitachi Medical Corporation, Tokyo, Japan). Then, the prongs of the needle electrode were deployed over a distance of 3 cm in all cases and the RF generator (RITA model 1500) (Fig. 1b) was activated and set to automatic, with power at 20 W, temperature of 95 °C, and an ablation time of 15 min. To prevent skin burns, 5% glucose solution was injected to increase the space between the skin and tumour, and a sterile ice bag was placed on the skin overlying the lesion during the ablation procedure. Subsequently, axillary lymph node dissection (ALND) was performed in patients with positive SLNs.

Histological and immunohistochemical evaluation of ablated tumours

Several months after RFA therapy, the ablated tumour tissue was obtained using a US-guided handy mammotome (Tyco Healthcare, Mansfield, MA). The specimen was divided into two parts: one was cut into frozen sections for nicotinamide adenine dinucleotide (NADH)-diaphorase staining, and the other was fixed in 10% neutral buffered formalin for histopathological examination with H&E staining and for immunohistochemistry to determine the expression of single-stranded DNA (ssDNA). These methods have been described elsewhere,\textup{19} although the NADH-diaphorase staining method was described in detail below. Histological evaluation with H&E staining was performed in accordance with the General Rules for Clinical and Pathological Recording of Breast Cancer: Histological Criteria for Assessment of Therapeutic Response in Breast Cancer.\textup{28} Expression of ssDNA was evaluated as positive or negative because positive cases showed diffuse staining in tumour cells, and positive expression on staining for ssDNA indicated non-viable cells.\textup{19}

NADH-diaphorase staining

For the NADH-diaphorase staining, the frozen tissue was cut into 6 µm non-fixed sections and placed on glass slides, and then placed in an incubation medium for 15 min under aerobic conditions at room temperature. The incubation medium consisted of 6.8 ml of reduced β-NADH-diaphorase (Sigma—Aldrich, St. Louis, Mo, U.S.A) at a concentration of 1.5 mg/ml, 12.0 ml of nitroblue tetrazolium chloride (Sigma—Aldrich, St. Louis, Mo, U.S.A) at a concentration of 2.0 mg/ml, 4.8 ml of phosphate-buffered saline, and 3.8 ml of Ringer solution.\textup{17} The pH of the medium was adjusted to 7.2 before the sections were incubated. After incubation, each slide was washed in distilled water for 2 min. After mounting the glass cover, slides were evaluated for characterization of staining within 24 h of processing.\textup{11} Intensive blue cytoplasmic staining in the cells was considered to indicate viable cell, whereas the absence of blue cytoplasmic staining indicated non-viable cell. A section of bile duct carcinoma tissue or normal skeletal muscle was used as the positive control for NADH-diaphorase staining. The border between blue-stained and unstained devitalized structures was delineated sharply, permitting an accurate determination of the extent of tissue necrosis.
Adjuvant therapies and follow-up

Postoperatively, all of the patients received breast radiation with high energy photons on the ipsilateral breast at a dose of 5000 rad through two opposing tangential fields, and adjuvant chemotherapy and/or hormone therapy after RFA, and were followed-up at the Breast Care Center, Yatsuo General Hospital or the Department of Breast and Endocrine Surgery, Kanazawa Medical University Hospital through April 2012. In all of the patients, physical examination, bilateral mammography, US, MRI, CT and/or positron emission tomography computed tomography (PET-CT) were performed 6 months after RFA and then annually thereafter.

On the other hand, cosmetic outcome of the conserved breast was assessed in comparison with the contralateral breast by one of the physicians (MN, ME, or AM). The assessment was based on the following criteria: volumetric symmetry of breasts, shape of breast mounds, symmetry of nipple-areola complex situation, and breast scar. The results were defined as excellent in cases in which the conserved breast was similar to the contralateral breast, good cases where there was a slight difference to the contralateral breast, and poor in which there were moderate or remarkable differences to the contralateral breast.29

Results

The characteristics of patients and tumours

During the study period, 18 patients with 19 tumours were treated with RFA followed by delayed US-guided mammo tomome biopsy, while one patient refused to undergo mammo tomome biopsy. One patient with bilateral breast cancer was counted as two cases in this study. The characteristics of the patients and tumours were summarized in Table 1. SLN biopsy was performed in all 19 cases, and ALND was subsequently performed in 4 cases because of positive SLNs. One patient was histologically found to have axillary lymph node metastases. All of the patients received RFA after SLN biopsy (Table 1).

Evaluation of breast tumour treated with radiofrequency ablation

From 24 to 202 days after the RFA (a median time: 30 days), a US-guided handy mammotome was used to obtain the ablated tumour and examine the presence of residual

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The characteristics of patients and tumours.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) No. of cases</td>
<td>19</td>
</tr>
<tr>
<td>(2) Age (years)</td>
<td>Range 22–59</td>
</tr>
<tr>
<td></td>
<td>Median 45</td>
</tr>
<tr>
<td>(3) Menopausal status</td>
<td>Pre 2</td>
</tr>
<tr>
<td></td>
<td>Post 17</td>
</tr>
<tr>
<td>(4) Tumour size on ultrasound (cm)</td>
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<tr>
<td></td>
<td>Median 1.3</td>
</tr>
<tr>
<td></td>
<td>≤1.0 6</td>
</tr>
<tr>
<td></td>
<td>1.1–1.5 8</td>
</tr>
<tr>
<td></td>
<td>1.6–2.0 5</td>
</tr>
<tr>
<td>(5) Histological type of primary tumour</td>
<td>Invasive duct carcinoma 18</td>
</tr>
<tr>
<td></td>
<td>Mucinous carcinoma 1</td>
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<tr>
<td>(6) Immunohistochemical type of primary tumour</td>
<td>Luminal A type 17</td>
</tr>
<tr>
<td></td>
<td>Basal-like type 2</td>
</tr>
<tr>
<td>(7) Axillary lymph node metastases</td>
<td>Negative 15</td>
</tr>
<tr>
<td></td>
<td>Positive 4</td>
</tr>
</tbody>
</table>
tumour cells in 18 of these cases. The ablated lesion was ultrasonographically identified in all except one case in which the patient refused to undergo mammotome excision and the ablated tumour subsequently became undetectable on US. Histologically, Grade 3 response (complete response) was observed only in 8 of 18 cases (44%) (Fig. 2a). However, NADH-diaphorase staining and/or ssDNA staining did not demonstrate any viable tumour tissue in the ablated region in 10 cases (Figs. 1c and 2b), although there were no tumour cells in the remaining 8 cases (Table 2).

Outcome of the patients

Although adjuvant chemotherapy was performed in 10 cases after mammotome excision, the remaining 8 cases underwent adjuvant chemotherapy or hormone therapy before mammotome biopsy in order to prevent the delayed administration of chemotherapy. As mentioned above, exceptionally, one patient received hormone therapy without undergoing mammotome biopsy. At a mean follow-up of 60 months (range: 37–82 months), none of the subjects developed in-breast recurrence, while one with extensive axillary lymph node metastases developed hepatic metastases and died 40 months after RFA therapy and ALND. However, a hard lump remained after RFA in 9 (47%) of 19 cases, although MRI showed no enhancement of the ablated lesion in any of the cases. Ultrasonographically, hypoechoic lesions ranging from 1.0 cm to 2.4 cm in diameter were observed in 15 cases, while no hypoechoic lesions were detected in the remaining 4 cases. There were no adverse effects, such as skin burns. The cosmetic results were assessed as excellent in 18 cases (Fig. 3), and good in the remaining one case because a skin dimple was observed on the breast due to mammotome excision (Table 2). Nevertheless, almost all of the patients were satisfied with the cosmetic results of conserved breast, because the conserved breast was similar to the contralateral breast.

![Figure 2](image)

Figure 2. Representative histological findings of ablated breast tumours. (a) H&E staining of the ablated tumour obtained by mammotome excision: Grade 1 response. (b) NADH-diaphorase staining of the ablated tumour: no viable tumour cells. (c) ssDNA staining of the ablated tumour: positive staining, non-viable.
Discussion

Is RFA therapy feasible in patients with small breast cancer?

RFA therapy is considered to be the most promising non-surgical ablation technique for the treatment of small breast cancer. Jeffrey et al. reported the first feasibility study of RFA therapy for breast cancer in 1999. Subsequently, several investigators have reported feasibility studies of RFA therapy for small breast cancer in the USA as well as Europe. In Japan, a number of investigators have commenced feasibility studies since 2003. These studies commonly suggested that RFA might be useful for the local control of small, well-localized breast cancer because of its effective cell killing ability in a reliable volume of tissue with a low complication rate. In the feasibility studies, however, the patients proceeded to definitive surgery. Thereby, the patients could not be followed-up for recurrence after RFA, or to determine if there were any undesirable side effects of the procedure.

Is RFA therapy without surgical resection oncologically safe?

Based on the results of these feasibility studies, several pilot trials have been performed to investigate the use of RFA without subsequent surgical resection. However, the follow-up periods are too short to allow investigation of breast recurrence and survival rates. Long-term follow-up of the patients treated with RFA is mandatory to evaluate the efficacy and safety of this therapeutic modality. To date, there has been only one study of the long-term outcomes of patients with primary breast cancer treated with RFA alone. Head et al. performed RFA successfully in 4 of 5 elderly patients with non-palpable breast cancers. While one patient underwent surgical resection after RFA, the other 3 patients were followed-up without surgical resection of the ablated tumour. They have shown no recurrence or continued growth of the lesion for up to 7 years after the RFA procedure. In the present study, we evaluated the oncological and cosmetic long-term outcomes in 19 cases undergoing this procedure. At a mean follow-up of 60 months, there have been no cases of in-breast recurrence, while one patient died due to hepatic metastases. Moreover, almost all of the patients were satisfied with the cosmetic results of conserved. Thus, our long-term study is encouraging with regard to cosmesis and local control.

What is a common problem of non-surgical ablation?

Non-surgical ablation techniques share a number of problems that remain to be resolved. Especially, the most prevalent concern regarding residual ablated tumour tissue in the breast is the need for assurance that all cancerous cells have been histologically destroyed. Nevertheless, histological evaluation by H&E staining was not reliable for tumour cell viability, although degenerative changes were more remarkable in cases with longer interval after RFA. It is well known that NADH-diaphorase staining is essential to assess the effects of RFA therapy. In the present study as well as the previous study, moreover, it was demonstrated that ssDNA staining is useful for the assessment of tumour cell viability after RFA therapy. However, a major argument against non-surgical ablation is the inability to assess the margins of the treated lesion, while there were no cases of in-breast recurrence in our series despite no assessment of the surgical margins. Breast cancer margins are difficult to determine and present perhaps the greatest challenge for imaging, and multiple core-needle biopsy also does not provide the margin status. Recently, Klimberg et al. advocated percutaneous excision followed by RFA of margins for the treatment of breast cancer. This treatment protocol allows removal of the lesion, full histopathology, and margin ablation under imaging guidance. Previously, we proposed a method of RFA followed by percutaneous excision of the ablated tumour using an Ovation breast biopsy device (Rubicor Medical, Redwood City, CA). However, this device is not commercially available in Japan.
What would be the potential hazards of RFA therapy?

No patients developed skin burns in the present study, although skin burns are commonly considered a major complication of RFA therapy. Injection of 5% glucose solution between the skin and tumour to increase the space, and placement of an ice bag on the skin overlying the lesion were effective for prevention of skin burn. However, a hard lump persisted in the treated breast after RFA in half of the cases. Although the ablated lump is not life-threatening, it can cause patient discomfort, anxiety, and fear. Recently, Yamamoto et al. reported that one patient suffered an adverse reaction in the ablated zone that was like chronic granulomatous mastitis, and consequently underwent partial mastectomy of the ablated lesion. However, Head et al. reported that the persistent mass after RFA is due to fat necrosis. They suggested that the palpable mass can be greatly reduced or even eliminated by (a) aspirating necrotic debris from the ablated area immediately postablation, (b) instilling steroid into the ablation cavity after aspiration, (c) administrating a depo-medrol dose pack postoperatively and mild antiinflammatory medications for 2 weeks postoperatively. This method may be useful not only to reduce or eliminate hard lumps but also to prevent adverse reactions in the ablated zone.

Finally, further studies are needed to establish the optimal technique of RFA, although our long-term study is encouraging with regard to cosmesis and local control. Moreover, a prospective study will be required to determine the equivalency in local recurrence rates between the RFA therapy and conventional BCT.

Conflict of interest

The authors have no potential conflict of interest.

References

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