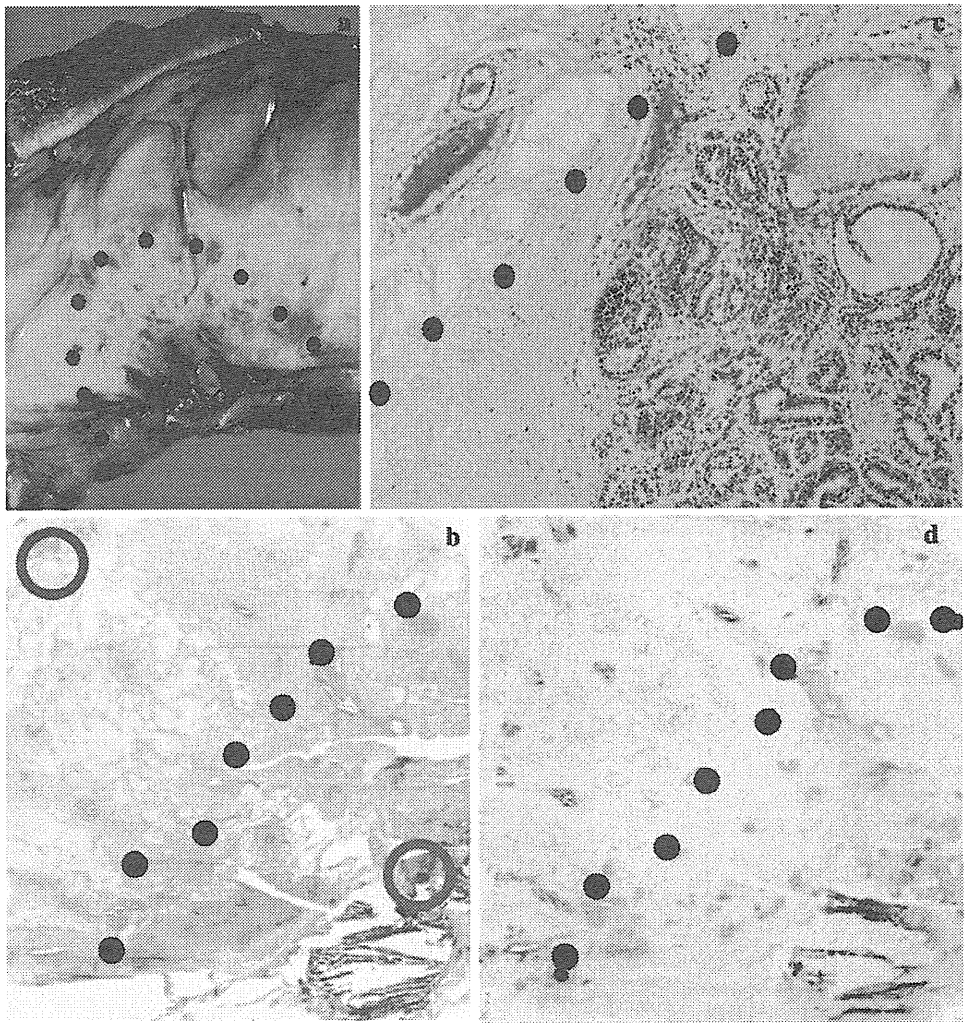

Fig. 4 Macro- and microscopic features of RFA-treated breast cancer and non-cancerous tissue. **a** Gross features of a mastectomized specimen resected immediately after the RFA procedure. The border between the ablated and non-ablated areas is delineated by a congestive limbic zone (indicated by *dots*). **b** The boundary between the ablated area (*right lower* to *dots*) and non-ablated area (*left upper* to *dots*). A low-magnification view of an HE-stained section. The control part of the ablated area (*red circle*) shows highly degenerative changes. **c** A higher-magnification view of the boundary between the ablated (*right lower* to *dots*) and non-ablated (*left upper* to *dots*) areas. In the latter, congestive blood vessels are evident. In the former, mammary tissue and stroma with mild to moderate heating effects are observed (HE). **d** The boundary between the ablated and non-ablated areas in the serial section of image **b**. The section was subjected to the NADH diaphorase reaction to color viable cells blue due to the reduction of NBT. Only the non-ablated area (*left upper* to *dots*) is stained blue

Microscopy examination

The boundary between the ablated and non-ablated area was identifiable histologically, although the effect of cautery showed a gradation from strong in the center to mild or moderate at the periphery (Fig. 4b, c). RFA damage to the epithelial cells and fibrous stroma in the ablated area was histologically visualized as follows in HE-stained sections. Epithelial cells, both cancerous and non-cancerous, were characterized by elongated eosinophilic cytoplasm with pyknotic "streaming" nuclei (Fig. 5b). The intercellular boundary and details of the nuclear and cytoplasmic texture were unclear. Fibrous connective tissue also showed degenerative changes resulting in dense homogeneous and highly eosinophilic features (Fig. 6). The original delicate, wavy structure had entirely disappeared. Fibroblasts in the area also showed thermal degenerative changes identical to those seen in epithelial cells.

At the periphery of the ablated area, epithelial cells showed coarse and plain nuclear chromatin due to the thermal effect (Fig. 5c). The boundary between ablated and non-ablated areas was usually characterized by congestive blood vessels, which were grossly evident as a red limbic zone (Fig. 4a). The effects of heating were sometimes relatively mild to moderate near the limbic zone, because the nuclear and cytoplasmic features characteristic of cell death at the periphery of the ablated area adjacent to the red zone were less marked (Fig. 5c) than those in the central ablated area.

Comparison between NADH diaphorase reaction and histopathological findings

Nicotinamide adenine dinucleotide diaphorase-stained sections showed no reaction in tumor cells at the center of the ablated area, where tumor cells and stroma showed marked heat degeneration. The border between the NADH diaphorase-positive and -negative areas was relatively clear and sharp (Fig. 4d). NADH-positive cells showed the fine structures of intact nuclear chromatin and cytoplasm

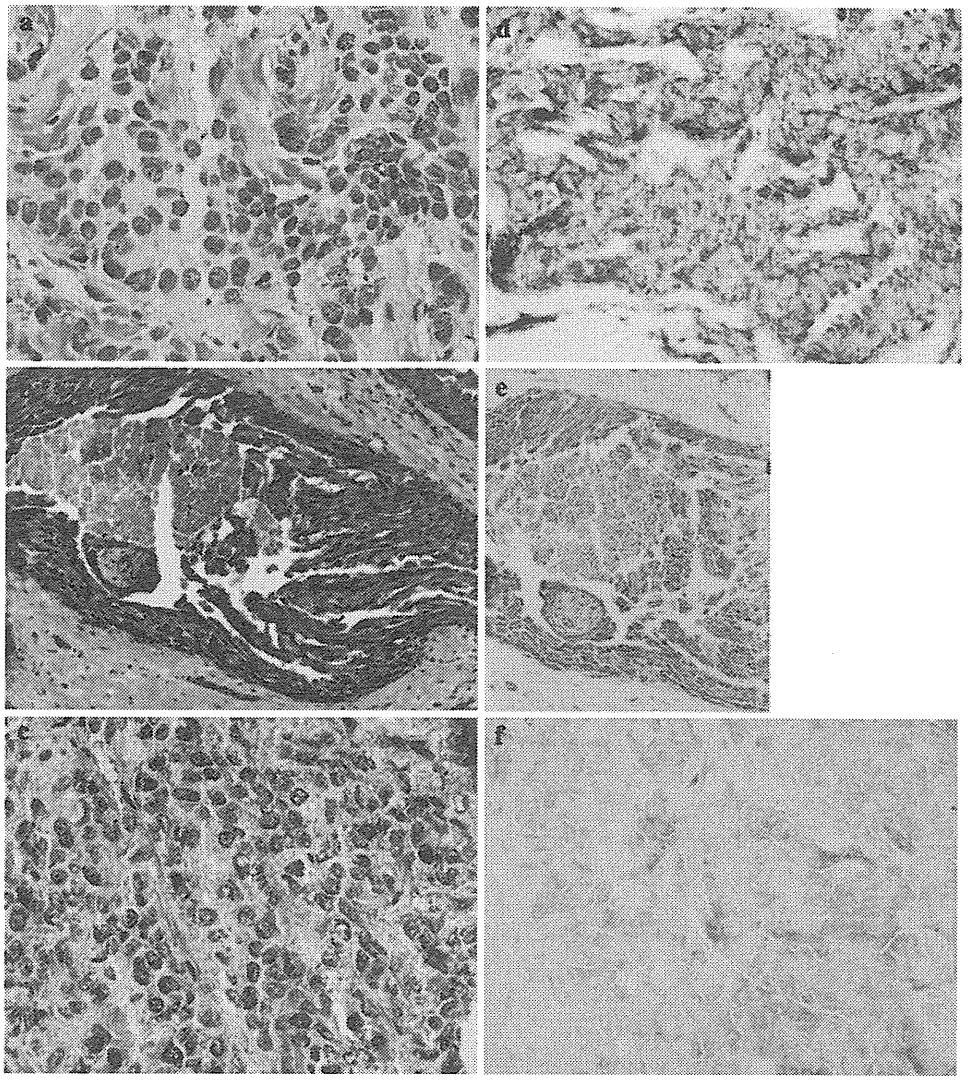

Fig. 5 Comparison of histopathological features of RFA-treated breast cancer tissue with histochemical results of NADH diaphorase staining. **a**, **d** A non-ablated invasive ductal carcinoma (control specimen). **b**, **e** An invasive ductal carcinoma showing a strong effect of RFA cautery. **c**, **f** An invasive ductal carcinoma showing a moderate heating effect of RFA. **a** Fine structure of the nuclei and cytoplasm of tumor cells, and the collagen fibers of the stoma, are preserved. **b** Ablated tumor cells show an elongated cytoplasm with "streaming-like" nuclei. **c** Ablated tumor cells are characterized by pale cytoplasm and rough chromatin in the nuclei with an unclear cellular border. **d** This carcinoma shows a positive NBT reduction reaction, staining the cells blue, indicating histochemical positivity for NADH diaphorase activity. **e** This carcinoma shows a negative reaction for NADH diaphorase, indicating an absence of viable tumor cells. An invasive ductal carcinoma showing a strong cautery effect of RFA. **f** This carcinoma shows a negative reaction for NADH diaphorase, indicating an absence of viable tumor cells

(Fig. 5a, b), surrounded by a fine, delicate fibrous stroma. In each tumor, the NADH-negative area was approximately equivalent to the area circumscribed by the congestive limbic zone. Neither the central area showing strong effects of cautery, nor the peripheral part of the ablated area showing less marked effects showed the NADH diaphorase reaction (Fig. 5d, f).

Discussion

We have described the macro- and microscopic findings characteristic of the cautery or heating effect of RFA, based on examination of specimens resected immediately after the procedure. The histopathological features of cellular damage described by some authors have included an unclear intercellular boundary, elongated eosinophilic cytoplasm, pyknotic "streaming" nuclei, and poorly defined nuclear and cytoplasmic texture [1, 4]. In addition, we found that the RFA procedure caused fibrous connective tissue to lose its delicate wavy structure and to degenerate to dense eosinophilic tissue with a loss of fine structure.

The area in which RFA was histologically effective was mostly concordant with the area of NADH diaphorase negativity, especially in the central part of the ablated area. At the periphery, however, cellular change caused by RFA was less marked, and the NADH diaphorase reaction visualized by NBT was usually negative. Fornage et al. described the histopathological changes observed in RFA-treated breast tissues in a study of 21 patients. The changes were similar to those observed in the present study, and were concordant with the results of NADH diaphorase staining [4]. However, a large number of cases should be studied in order to establish criteria for the histopathological effect of RFA. Although the histochemical assay for NADH diaphorase activity is reliable, it cannot always be performed in routine practice. It will therefore be necessary

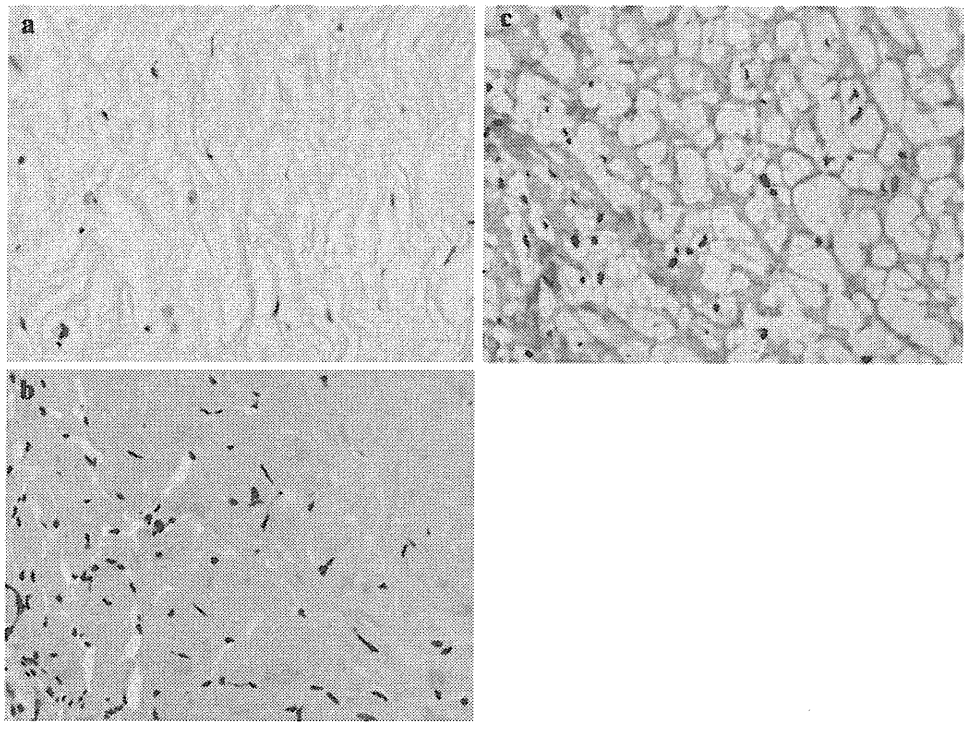

Fig. 6 **a** Non-ablated stromal tissue in the breast demonstrates the fine wavy structure of collagen fibers (control specimen). **b**, **c** A highly ablated stroma showing eosinophilic and amorphous features without a fine wavy texture. Nuclei of fibroblasts are also pyknotic

to standardize criteria for the effects of RFA that are applicable to formalin-fixed and paraffin-embedded tissue sections.

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Radiofrequency ablation as local therapy for early breast carcinomas

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Abstract
Purpose To evaluate the safety and efficacy of radiofrequency ablation (RFA) as a local therapy for early breast carcinomas, we performed a phase I/II study at our institution.
Patients and methods Fifty patients with core-needle biopsy-proven breast carcinoma that was ≤3 cm in diameter on ultrasonography were enrolled in this study. Under ultrasound (US) guidance, the tumor and surrounding breast tissue were ablated with a saline-cooled RF electrode followed by immediate surgical resection. Resected specimens were examined by hematoxylin and eosin (H&E) staining and nicotinamide adenine dinucleotide (NADH) diaphorase staining to assess tumor viability.
Results Forty-nine patients completed the treatment. The mean tumor size was 1.70 cm. The mean ablation time was 8.7 min using a mean power of 48.5 W. Of the 49 treated patients, complete ablation was recognized in 30 patients (61%) by H&E staining and/or NADH diaphorase staining. The NADH viability staining was available for 38 patients, and in 29 (76.3%), there was no evidence of viable malignant cells. Of the 29 treated patients with breast carcinomas ≤2 cm in diameter examined by pathological examination, complete ablation was achieved in 24 patients (83%). Of the 26 treated patients with breast carcinomas without an extended intraductal component (EIC) according to pathological examination, complete ablation was determined in 22 patients (85%). RFA-related adverse events were observed in five cases: two with skin burn and three with muscle burns.
Conclusion RF ablation is a safe and promising minimally invasive treatment for small breast carcinomas with pathological tumor size ≤2 cm in diameter and without EIC.

Keywords Radiofrequency ablation · Local therapy · Early breast carcinomas · Phase I/II study

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Introduction

There has been a change in the management of cancer patients with localized disease from total mastectomy to lumpectomy complemented by adjuvant radiotherapy and chemo-endocrine therapy, without significant outcome [1, 2]. Early detection of small breast lesions may further change the attitude toward less invasive and even non-invasive management [3].

A major goal of breast-conserving treatment is the preservation of a cosmetically acceptable breast. Although a variety of patient and treatment factors have been reported to influence the cosmetic results, the amount of breast tissue resected appears to be a major factor [4]. Several investigators are studying the feasibility of percutaneous minimally invasive techniques to ablate breast tumors. Several modalities, such as cryosurgery, laser ablation, thermoablation, and high-intensity focused US, have been investigated [5]. By minimizing damage and

disruption to normal surrounding tissue, the morbidity of local treatment, such as scarring and deformity, can be reduced, and the cosmetic results can potentially be improved. With the widespread application of screening mammography, the mean size of the breast tumors detected has continued to decrease, which further emphasizes the need for less invasive means for achieving local tumor destruction, such as RF ablation [6].

The aim of this phase I/II study was to determine the safety and efficacy of radiofrequency ablation (RFA) of early breast carcinomas using saline-cooled electrodes. Our secondary goals were to determine the size, configuration and pathological features of acute RF ablative treatment of breast carcinomas.

Patients and methods

Patients

All patients had a prior histological diagnosis of breast cancer established by stereotactic or US-guided core biopsy. Core biopsy had to be adequate for routine pathological evaluations (grade, estrogen receptor, progesterone receptor, Her 2-neu) because after RF ablation has been performed, viable tumor may not be available for these analyses.

Eligibility criteria included age between 20 and 90 years and tumor size $\leq$3.0 cm in diameter on US examination. Patients were excluded if there was evidence of diffuse calcification suggestive of extensive multifocal ductal carcinoma in situ of more than 3.0 cm in size.

MRI was performed on all patients to evaluate the lesions more precisely and compared with the results of RF ablation. Patients treated with preoperative chemotherapy were excluded. This study was approved by the National Cancer Center, Japan Institutional Review Board, and all patients provided written informed consent.

Treatment

All patients underwent breast US and MRI preoperatively to determine if the tumor was visible in order to facilitate US-guided RF ablation. The patient could elect to undergo either a lumpectomy or a mastectomy as in both situations the RF ablated tissue would be available for pathological review. Sentinel lymph node biopsy (SLNB) was performed for axillary staging. Tracers for SLNB were injected into the subareolar parenchyma to prevent the interference of air/fluid with intra-operative US imaging.

After general anesthesia was induced and SLNB was completed, the breast tumor was identified with intraoperative US using the Toshiba Aplio XG SSA-790A (Toshiba Medical Systems Corporation, Otawara, Japan) with a PLT-1204AT (2D, 12 MHz) and a PLT-1204MV (4D, 14 MHz) probe. Under US guidance, the 17-gauge Valleylab^{TM} RF Ablation System with Cool-tip^{TM} Technology (Covidien, Energy-Based Devices, Interventional Oncology, Boulder, CO) was inserted in the center of the tumor (Fig. 1). With US imaging in the two planes, we ensured that the electrode was located in the center of the lesions using a linear 2D probe for the vertical image and 4D probe for the coronary image (Fig. 2). In all cases, a 2-cm active tip electrode was used. Before ablation, we injected 20 to 40 ml of 5% glucose to avoid skin or muscle burn. The needle electrode was attached to a 500-kHz monopolar RF generator capable of producing 200-W power. Grounding was achieved by attaching two grounding pads to the patient's thighs before the producer. Tissue impedance was monitored continuously using circuitry incorporated into the generator. A peristaltic pump (Watson-Marlow, Medford, MA) was used to infuse 0°C normal saline solution into the lumen of the electrode at a rate sufficient to maintain a tip temperature of 15–25°C.

RF energy was applied to tissue with an initial power setting of 10 W and subsequently increased with increments of 5 W each minute to a maximum power of 55 W. Saline circulating internally within the electrode cools the adjacent tissue, maximizing energy deposition and reducing tissue charring. The power setting was left at this point until power 'rolloff' occurred. Power rolloff implies that there is an increase in the tissue impedance caused by loss of sodium chloride, which occurs with tissue coagulation around the monopolar electrode. When this occurs, the power generator will shut off, stopping the flow of current and further tissue coagulation. After waiting 30–60 s, the second phase was started at 75% of the last maximum power until a second rolloff occured. The appearance and progression of hyperechogenicity on US were used to guide the therapy. Radiofrequency was applied until the tumor was completely hyperechoic (Fig. 3). To minimize thermal injury to the skin, sterile ice packs were placed on the breast during the ablation procedure (Fig. 4). Following RF ablation, standard tumor resection was achieved with either a wide local excision or mastectomy according to the preference of the patient. The surgical specimen was obtained and immediately sent fresh to the pathology department.

Pathological evaluation

Frozen section

Specimens resected by the surgeons were submitted to the pathologists for nicotinamide adenine dinucleotide

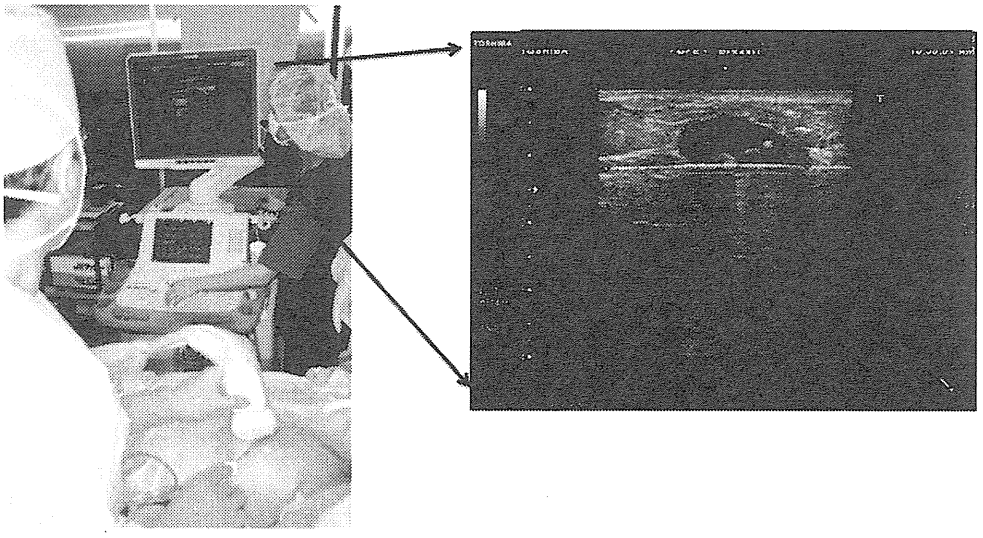

Fig. 1 Technique for performing breast radiofrequency ablation (RFA). Under ultrasound guidance the RF electrode is percutaneously inserted into the breast tumor. The needle is seen transversing the target tumor

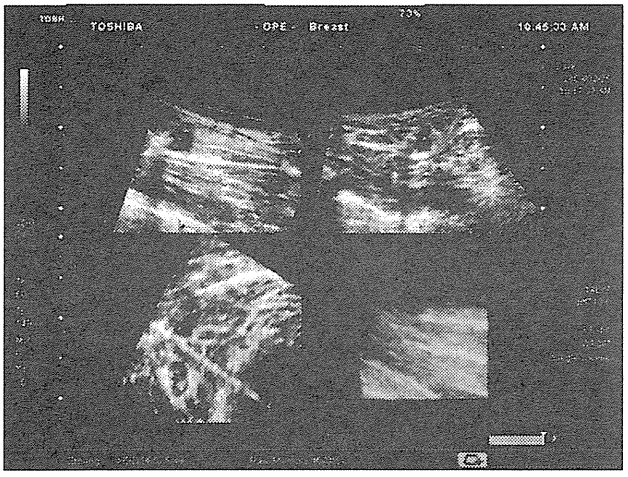

Fig. 2 Confirmation of the location of the needle using a 4D probe. With ultrasound imaging in the two planes, we ensured that the electrode was located in the center of the lesions using a linear 2D probe for the vertical image and 4D probe for the coronary image

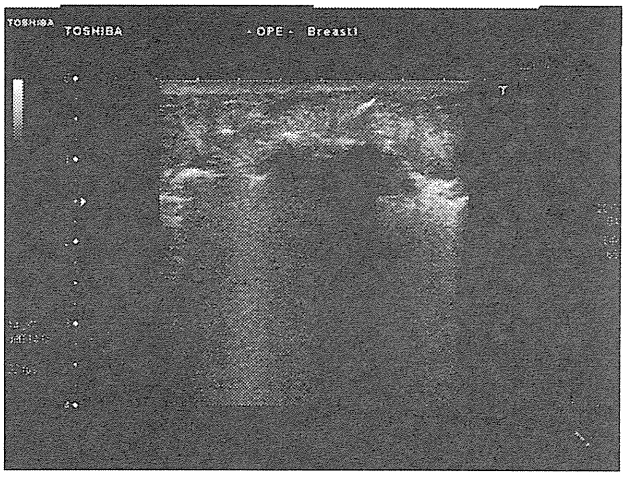

Fig. 3 Intraoperative breast ultrasound. Radiofrequency was applied until the tumor was completely hyperechoic

(NADH) diaphorase cell viability analysis and routine histopathological examination. A tissue slice including the representative cut surface of the tumor and non-ablated mammary glands was removed and subjected to frozen section preparation.

One to two pieces of representative tumor tissue and another piece of non-ablated mammary gland were snap frozen in liquid nitrogen and cut into 5-μm-thick sections using a cryostat (Shiraimatsu, Tokyo, Japan). One of the sections was stained with H&E and was microscopically confirmed to contain the representative tumor tissue and non-ablated mammary gland tissue. Other sections were stored at −20°C until NADH diaphorase assay.

Fig. 4 Skin protection. Skin is protected by the placement of an ice pack during the RFA procedure

Histological analysis

From residual tissue specimens, an entire representative cut surfaces of the ablated tumor and surrounding tissue were taken as tissue blocks for histopathological examination. The blocks were formalin-fixed, paraffin-embedded and cut into 3- to 4-μm-thick sections. These sections were stained with HE. Histopathologically, the viability of tumors was evaluated in consideration of thermocautery artifacts. When the degeneration was marked in cancer cells, the effect of thermocautery was effective. The tumor area with marked degeneration was calculated for each case.

Immunohistochemically, expression of estrogen receptor (ER, clone ID5 clone, Dako, Glostrup, Denmark), progesterone receptor (PR, clone IA6, Dako) and HER2 (Herceptest, Dako) were examined. For ER and PgR, a tumor was judged as positive if 10% or more of the tumor cells showed positive nuclear immunoreactions irrespectively of the intensity of the immunoreactions. For HER2, judgment about immunoreactions was made according to the recommendations of the ASCO/CAP guidelines.

NADH diaphorase cell viability analysis

The enzyme histochemical analysis of cell viability was performed based on the reduction of nitroblue tetrazolium chloride, a redox indicator, by NADH diaphorase, resulting in an intense blue cytoplasmic pigmentation. The activity of this enzyme has been shown to subside immediately upon cell death. For this analysis, 5-μm cryostat-cut unfixed sections were placed in a coprin jar and incubated in 0.05 M tris-buffered saline (TBS, pH 7.4) containing 500 mg/l tetranitro blue tetazolium and 800 mg/l β-NADH (Sigma-Aldrich Corp., St. Louis, MO) for 30 min at 37°C. Thereafter, the sections were fixed in 10% formalin for 30 min, washed with distilled water for 2 min and mounted with a cover glass. Based on the area of cells with blue cytoplasmic staining, the viability of tumor cells and non-ablated mammary gland cells as control was evaluated.

Results

Fifty patients were enrolled in the study, and 49 completed RF ablation therapy. For one patient, the ablation system had some trouble, and we decided not to proceed with the therapy. The patient demographics of the 49 patients who received the proposed RF ablation therapy are shown in Table 1. The median age was 61 years (range 36–82). The median breast tumor size based on the ultrasonographic maximum dimension was 1.70 cm (range 0.5–3.0). The histology was invasive ductal carcinoma for 43 patients (88%).

Table 1 Patient demographics of 49 patients

	Number of patients
Age (years)	
Median	61
Range	36–82
Method of diagnosis	
Mammgoram screening	32 (65%)
Palpable mass ± mammogram	17 (35%)
Tumor classification	
Tis	1 (2%)
T1	34 (69%)
T2	14 (29%)
Tumor location	
Upper outer	18 (37%)
Lower outer	5 (10%)
Upper inner	18 (37%)
Lower inner	7 (14%)
Central	1 (2%)
Tumor size on US (cm)	
Median	1.70
Range	0.5–3.0
Tumor size on MRI (cm)	
Median	1.50
Range	0.7–4.5
Lymph node status	
N0	44 (90%)
N1	5 (10%)

RF ablation time ranged from 3–18 min (mean 8.7 min). Mean tumor impedance was 195.1 Ω, and for 4 of 49 patients, there was a reduction in the impedance during treatment by a mean of 53.4 Ω.

A median of one cycle and a mean power of 48.5 W (range 5–118 W) were used to achieve tumor ablation.

RFA of the breast tumor was monitored with ultrasonography every 3 min.

In 49 patients, as tumor heating around the multiple array electrodes developed, an ill-defined, hyperechoic zone developed. The size of the ablation measured by ultrasonography ranged from 15 to 50 mm (mean 27.3 mm).

RFA-related adverse events were observed in five cases (10%): two with skin burns and three with muscle burns. The entire skin burn area was excised during the breast tumor resection, and the patient had no further sequelae. These events occurred in initial cases. So, in order to avoid these burns, 10 ml of 5% glucose was injected between the skin and tumor, and also between the muscle and tumor. Since then, no skin burns have been observed.

There was no bleeding from the needle track upon removal of the RFA needle electrode in any of the 49 patients.

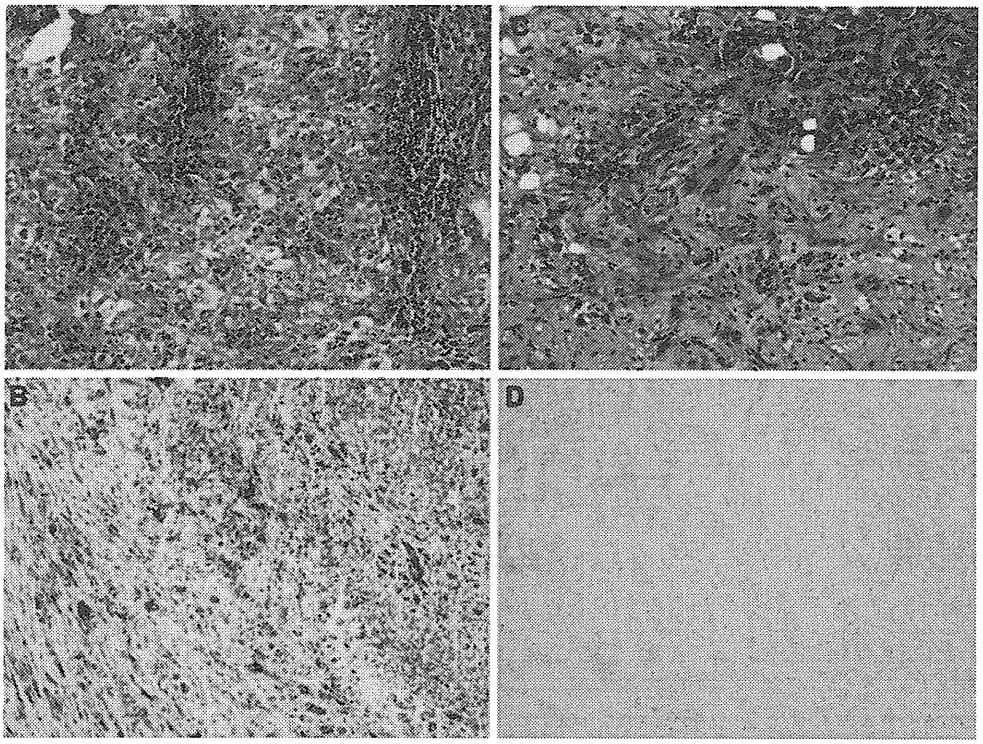

Fig. 5 NADH viability study. **a** H&E section of non-ablated breast tumor; **b** NADH viability study of non-ablated breast tumor T; **c** H&E section of ablated breast tumor; **d** NADH viability study demonstrating non-viable ablated tumor (magnification ×200)

Surgical resection consisted of total mastectomy in 27 patients, whereas 22 patients underwent wide local excision. In the early stages of this study, we selected the patients with small breast cancers who prefered to be treated by mastectomy.

On H&E examination, the tumor architecture was maintained despite ablation, which allowed the pathological size to be assessed accurately. The RFA-treated carcinomas showed a range of pathological findings. All of the treated tumors showed elongated nuclei with smudged chromatin (Fig. 5c). All cases showed extensive electrocautery changes with densely eosinophilic stromas.

In resected samples ablated with a 2.0-cm active tip of the electrode, the results of H&E and NADH examination showed that the mean diameter of the major axis was 3.0 cm (range 0–6.6 cm) and of the minor axis 2.2 cm (range 0–6.6 cm) (Table 2).

NADH viability staining was available for 26 patients, and in 20 (76.9%), there was no evidence of viable malignant cells (Fig. 5d).

Among cases of tumor diameter less than 2 cm in pathological examination, the NADH viability staining was available for 22 patients, and in 20 (90.9%), there was no evidence of viable malignant cells. The two viable cases were due to insufficient ablation; the reason for one case was a defective device and for another case was that the impedance was too high for the tumor to be ablated completely.

In H&E examinations, all tumors diagnosed with non-viability with NADH staining had confirmed changes with characteristics, i.e., amorphism, in the interstitial cells, linear form, rarefaction and inspissation in the nucleus of epithelial cells, etc.

Among most of the cases with viable malignant cells diagnosed with NADH staining, each tumor diameter was nearly 3 cm. Only one case had incomplete ablation of the index tumor because the tumor was eccentric within the RFA zone.

In total, on H&E and or NADH staining, 18 patients (37%) in 49 RFA cases had some viable invasive or in situ disease seen in the surgical excision specimen.

Table 3 shows treatment results depending on the pathological tumor size, including both invasive and intraductal lesions measured in surgical excision specimens. Out of 29 cases with tumor diameters $\leq$2 cm in pathological examination, 25 (86%) had confirmed complete ablation. In 20 cases of tumor diameter >2 cm, only 6 cases (30%) showed confirmed complete ablation. Table 4 indicates that the treatment result also depended on the existence of an extended intraductal component (EIC) of the tumor in the surgical excision specimen. In 26 cases of tumor without EIC in pathological

Table 2 Pathological findings for 49 patients

	Number of patients
Tumor type	
Invasive ductal	43 (88%)
Invasive lobular	1 (2%)
Mucinous	2 (4%)
Medullary	2 (4%)
DCIS	1 (2%)
Tumor grade	
1	22 (45%)
2	16 (33%)
3	11 (22%)
Pathological nodal status	
Negative	39 (80%)
Positive	10 (20%)
Pathologic tumor size (cm)	
Median	1.7
Range	0.1–8
Extended intraductal component (EIC)	
Present	23 (47%)
Absent	26 (53%)
Pathologic response to RFA	
Longest diameter of ablation zone (cm)	
Median	3.0
Range	0–6.6
Shortest diameter of ablation zone (cm)	
Median	2.2
Range	0–6.6
Incomplete tumor ablation	19 (39%)
Residual INV	8 (16%)
Residual DCIS	11 (23%)

RFA Radio frequency ablation

Table 3 Correlation between pathological tumor size and tumor ablation

Pathological tumor size (cm)[a]	No. of patients	Complete tumor ablation (%)	Incomplete tumor ablation (%)
≤2	29	25 (86)	4 (14)
>2	20	6 (30)	14 (70)

[a] Size of invasive and DCIS

Table 4 Correlation between existence of EIC and tumor ablation

	No. of patients	Complete tumor ablation (%)	Incomplete tumor ablation (%)
EIC present	23	9 (39)	14 (61)
EIC absent	26	22 (85)	4 (15)

EIC Extended intraductal component

examination, 22 (85%) had confirmed complete ablation. In 23 cases of tumor with EIC, only 9 (39%) had confirmed complete ablation.

According to these results, pre-RFA MRI detection with ultrasonography should be examined to detect the EIC of the tumor, and appropriate cases for RFA must be determined.

Discussion

Radiofrequency ablation is mainly used in clinical practice to treat unresectable hepatic tumors, and so far experience with breast carcinomas is limited [7–12].

RFA causes local tumor cell destruction by thermal coagulation and protein denaturation [5, 7, 13]. The higher the target temperature, the less exposure time is needed for cellular destruction [14, 15]. Cell death occurs above 45–50°C approximately. The target temperature mostly used at the tip of the prongs was 95°C and was maintained around 15 min [16]. It is conceivable that this setting could result in melting the fatty tissue, with bad cosmetic results. However, the lesions might be destroyed equally well with a lower target temperature and shorter ablation time [8].

Clearly, more research on the radiofrequency dose and effect is necessary to optimize RFA in breast carcinomas.

The shape, size and design of the RF electrode determined the shape of the ablation zone and, in the end, the success of the procedure. Because the size of the thermal lesion is limited using a single-needle electrode, multiarray electrodes have been developed that can produce thermal lesions of 3–5 cm in diameter.

In our trials, the ablation zone with a 2-cm active tip of the electrode had the following characteristics: the mean diameter of the major axis was 3.0 cm (range 0–6.6 cm) and that of the minor axis was 2.0 cm (range 0–6.6 cm).

However, some studies reported the distance between the tumor and the skin and the chest wall should be at least 1 cm because of possible burning of normal tissue. Lateral compression of the breast during the entire ablation procedure or ice cooling in cases of borderline distance to the skin is also essential to prevent possible skin burns [7, 8].

However, using a 5% glucose injection between the skin and tumor, and between the chest wall and tumor, and cooling skin with ice in order to avoid these burns, a tumor diameter less than 1 cm could be achieved with RFA.

The difficulty in assessing the margin of the ablated lesions is a limitation in all percutaneous ablation techniques. To minimize the risk of local recurrence and to make sure the whole tumor and safe margin are ablated, the lesions need to be excised with a rim of at least 1 cm.

After excision, tumor viability is tested by NADH diaphorase. Almost every study described immediate

excision of the ablated lesion [8, 10–12]. Burak et al. and Hayashi et al. [1, 9] had an interval of 1–3 weeks before excising the ablated zone. It was hypothesized that due to the effect of local vessel thrombosis and necrosis of surrounding tissue, the ablated zone expands in the period of time and provides a more accurate excision. In the end, the two trials did not have higher percentages of complete tumor ablation compared to the other studies, and it was concluded that an interval time between ablation and excision of the tumor might not be necessary [7, 9].

In cases of tumor diameter less than 2 cm, the NADH viability staining was available for 22 patients, and in 20 (90.9%), there was no evidence of viable malignant cells. The other two viable cases were due to insufficient ablation; the reason for one case was a defective device and for another case that impedance was too high for the tumor to be ablated completely. Breast cancer tissue is usually composed of tumor, normal tissue, fat, vessels, etc., and shows heterogeneity. The fat tissue has one of the highest electrical resistances. High resistance mean less effect from electrical power, such as radiofrequency. Therefore, we suspect that in our cases the component with high impedance against RFA might be fatty.

Up until now, only one pilot study has been performed that tested RFA in three elderly patients with breast cancer without excision of the ablated zone [17]. All three patients completed the treatment without complications, and after 18 months of follow-up, no recurrence had occurred. In the future, if RFA is to be used as a replacement for surgery, CNB might also be an option to confirm successful ablation. Fornage et al. suggested that multiple core-needle biopsies through the ablated lesion and its periphery should be obtained 3–4 weeks after the RFA procedure.

An indication for RFA can be early breast cancer ($T \leq$ 2 cm). In 29 cases of tumor diameter $\leq$2 cm, 25 (86%) were confirmed to have complete ablation (Table 3). In 26 cases of tumors without EIC in pathological examination, 22 (85%) were confirmed to have complete ablation. In 23 cases of tumor with EIC, only 9 (39%) were confirmed to have complete ablation. According to MRI detection, tumor diameter and the EIC could be evaluated more accurately. Appropriate cases for RFA should be selected deliberately after enough diagnosing with US and MRI detection concerning the diameter, type, EIC, multiple lesions, etc.

The optimal conditions for RFA correlate to results under the following conditions: (1) tumor diameter <2 cm diagnosed with US and (2) <2 cm except for multiple lesions and extended intraductal spread of lesions of more than 2 cm diagnosed with MRI detection.

Also, in two cases, the tumor body could not be ablated sufficiently. Effects of RFA depend on tissue resistivity, so fatty tissue and tumor components can affect these effects. Components of breast carcinoma are different for each patient, and further studies are needed. In cases in which the initial resistance is too high and rolloff occurs immediately, as our study showed, the target temperature cannot be reached, and procedures should be changed from RFA to lumpectomy for the patients' safety. The reasons for these incidents need to be examined with resected samples.

In Japan, RFA is a popular treatment method for liver cancer.

Half of liver cancer patients are treated by RFA. This system is familiar to many physicians even in local hospitals and clinics.

Although cryoablation and the HIFU have not been approved by the Japanese government, only RFA has been approved and has the possibility to be admitted as an option for local treatment.

RFA seems to be a promising new tool for a minimally invasive procedure for small breast carcinomas. However, follow-up data regarding the local effects on the surrounding breast tissue or recurrence rates are hardly available. Further research will be necessary to establish the optimal technique and to demonstrate the long-term oncological and cosmetic effects of RFA.

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I. RFA

1. 乳癌に対する熱凝固療法の適応と限界—RFAを中心に—

Feasibility study on radiofrequency ablation for small breast carcinomas and future study

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Summary

乳癌の外科治療は乳房温存手術やセンチネルリンパ節生検法がすでに標準化している。本邦においても乳癌の罹患率が上昇するとともに，マンモグラフィ検診の普及や画像診断法の進歩により，早期乳癌の発見機会の割合が増加してきている。このような時代的背景と患者の要望に応えるため，さらなる低侵襲局所治療であるnon surgical ablation療法が注目されはじめた。実臨床で乳癌に応用されているのは凍結療法（cryoablation），MRガイド下集束超音波療法（MRgFUS），ラジオ波熱凝固療法（radiofrequency ablation：RFA）であるが，装置の普及度と簡便さからRFAが急速に普及していった。一方，われわれの施設では2006年より高度医療評価制度下に早期乳癌に対するRFAの多施設臨床試験を実施し，その適応と限界を明らかにしてきたので紹介する。

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Key Words　乳癌，ラジオ波熱凝固療法，高度医療評価制度，安全性試験

はじめに

早期乳癌の局所療法としての乳房温存療法は，本邦では1980年代から慎重な適応基準をもって導入されたが，術前化学療法を併用するなどにより徐々に適応を拡大し，現在では約6割の患者が恩恵を受けている。一方，究極の乳房温存療法としてのnon surgical ablation therapyが試みられてきている。RFAの原理は交流電流により電極周囲の組織にイオンの変動が起き，その結果として生じる摩擦熱により癌細胞を凝固，壊死させるものである。本稿では，高度医療評価制度下に実施している当院でのRFA安全性試験の

◆メモランダム◆

クールチップRFシステムの原理と機能

AMラジオに近い周波数の電流を組織に流し，通電加熱の原理にてジュール熱を発生して組織を焼灼する。組織における熱の影響は50℃で不可逆的組織変性が始まり，100℃にて組織炭化・蒸散発生する。RFAの最終目標組織温度は60℃以上である。

本システムの特徴を以下に示す。

・針先の温度センサーにより，焼灼後の組織温度を測定できる。ただし，焼灼中は，針の中を水が通るため（炭化防止），測定不能。

・インピーダンスコントロールモード（※）により，焼灼効果を高めることができる。

※抵抗値が，初期抵抗より20Ωあがったとき，自動的に出力が0.005Aになる状態が15秒間続く（ブレイクまたはロールオフと呼ばれる）。ブレイク後は，ふたたびブレイク前の出力で再開。焼灼により高まった組織抵抗をいったん抑え，さらなる焼灼効果を狙う。

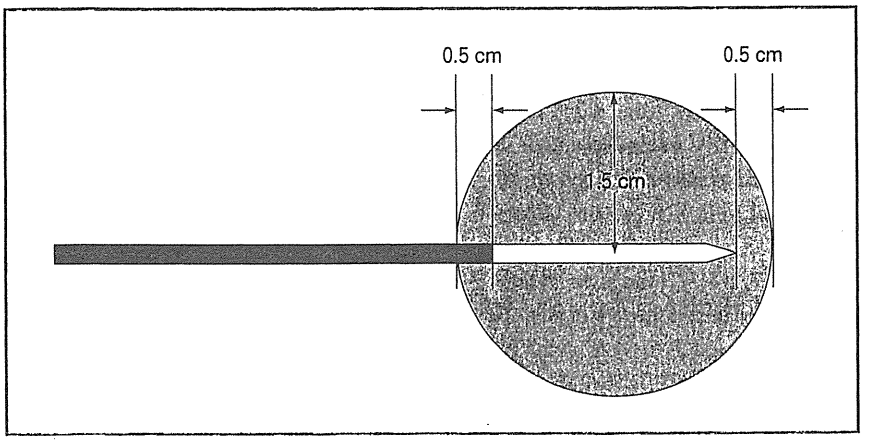

図1　肝臓癌でのRFA — Cool-tipニードルの焼灼範囲（参考：肝臓）

17GのCool-tip RFシステムシングルニードルは，症例の焼灼径に合わせ，exposure size（白色部）を1 cm，2 cm，3 cmと選択できる。グレーが焼灼範囲。

概要と今後の問題点について解説する。

本邦におけるRFAの現状

RFAは国内では肝臓癌の治療として用いられている。Cool-tipニードル（17G）での肝臓における焼灼モデルを図1に示した。exposure size 1.5 cmを選択した場合，直径3 cmの範囲が焼灼されることになる。この手技を乳癌に応用したもので，当初，肝臓と同じ7本の展開針型ニードルが用いられていたが，乳腺組織が肝臓と比べて硬く，穿刺しにくいこと，皮膚への熱伝搬のコントロールが難しいことなどから，現在ではシングルニードルで熱コントロールも容易なCool-tip RF System（COVIDIEN, energy-based devices, Interventional Oncology, Boulder, CO, USA）が主に用いられている。

本法の利点としては，肝臓癌治療ですでに普及している機器を使用するため，機器を有する施設ではニードルの購入のみで実施できるので，わが国では普及する可能性が高い。欠点としては，局所の疼痛が強いため全身麻酔下での実施が推奨されること，治療中に組織内に水蒸気（バブル）が発生するため超音波検査での治療領域の観察が困難であること，局所反応が強いため局所の一過性の浮腫や硬結の残存を認めることなどが挙げられる。

2010年度に日本乳癌学会にて実施されたアンケート調査によると，乳癌に対するRFAは国内29施設が実施し，症例数は1,049症例であることが判明した。ただし適応や標準的手技，管理体制がまちまちで，臨床試験として実施していない施設も少なからず認められた。これに対して日本乳癌学会では乳癌RFAは臨床試験として実施するようにと警告した。また，乳癌低侵襲治療研究会では，患者のフォローアップデータやQOLに関しても検証の必要があると考え，調査を行っている。

当院におけるRFAの実際

当院では，2006年6月より倫理審査委員会の承認の下に，RFAの安全性とRFA施行後に切除標本にて病理組織学的に評価を行う安全性試験を開始した。primary endpointは手術手技の確立と有害事象の評価，secondary endpointを抗腫瘍効果の評価方法として，目標症例数は40例として開始した。本研究は，厚生労働省の臨床的使用確認試験として開始し，高度医療（第三項先進医療）へと引き継がれて実施された。最終的に50例登録され，49例に対して治療が行われた。対象症例を表1に示した。試験開始当初は，施術後，乳房切除の症例を対象としたため腫瘍径3 cmまでを適応としている。画像診断では，超音波検査（US）およびMRIを必須として，腫瘍径の計測はUSを基本とした。

当院での手技は，USガイド下に経皮的にCool-tipニードル（17G）を腫瘍の中心部に留置する（図2）。皮膚熱傷の予防のために，RFA前に腫瘍の皮膚側と筋肉側に5％ブドウ糖液を注入し，さらに施術中は氷嚢にて十分に皮膚を冷却する。施術中はUSにて適

表1　患者背景

	症例数
年齢（歳）	
中央値	61
レンジ	36～82
診断方法	
マンモグラフィ検診（症状なし）	32(65%)
自覚症状あり	17(35%)
T分類	
Tis	1(2%)
T1	34(69%)
T2	14(29%)
占拠部位	
C	18(37%)
D	5(10%)
A	18(37%)
B	7(14%)
E	1(2%)
US腫瘍径（cm）	
中央値	1.70
レンジ	0.5～3.0
MRI腫瘍径（cm）	
中央値	1.50
レンジ	0.7～4.5
臨床的リンパ節転移（N）	
N0	44(90%)
N1	5(10%)

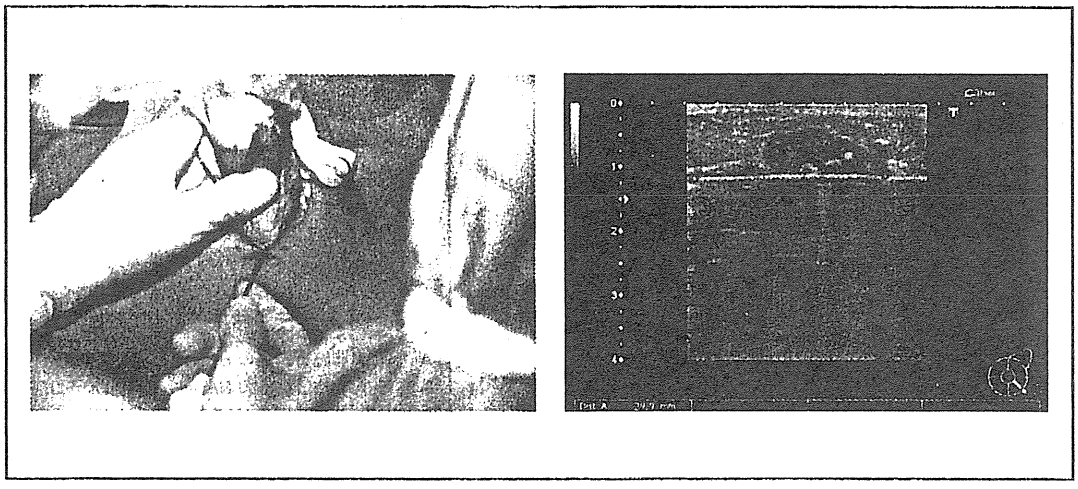

図2　電極針をUSガイド下に穿刺

超音波ガイド下にCool-tipニードルを腫瘍の中心を貫くように穿刺する。その際にニードルの先端から腫瘍の両側端（近位，遠位）までの距離を計測し，記録しておく。

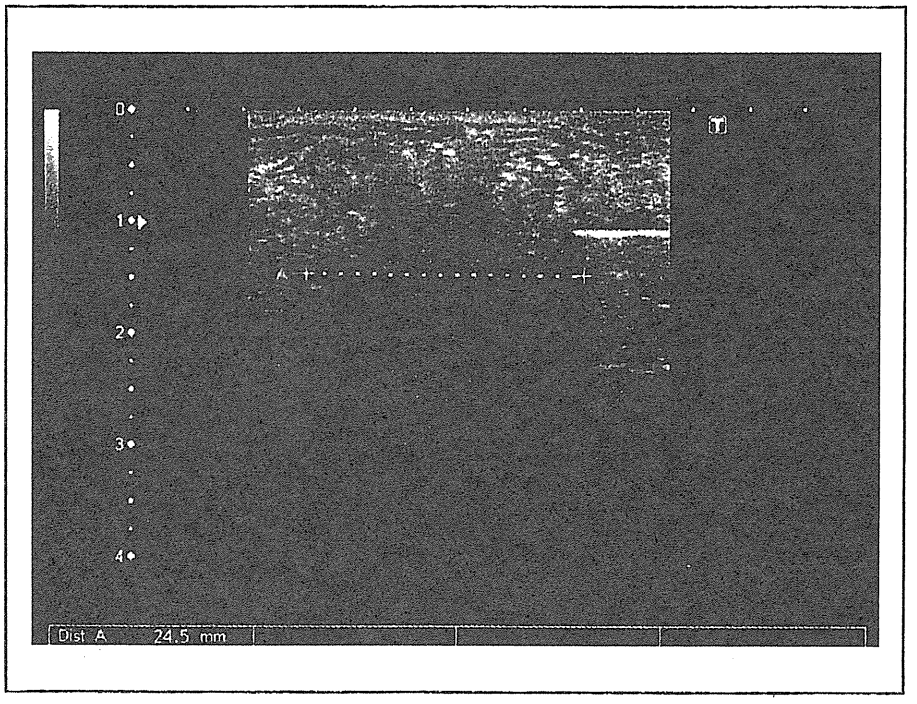

図 3　RFA 終了時の腫瘍超音波像

RFA 終了後，腫瘍影は熱変性したバブル像に置き換わる。この熱変性領域を計測しておく。

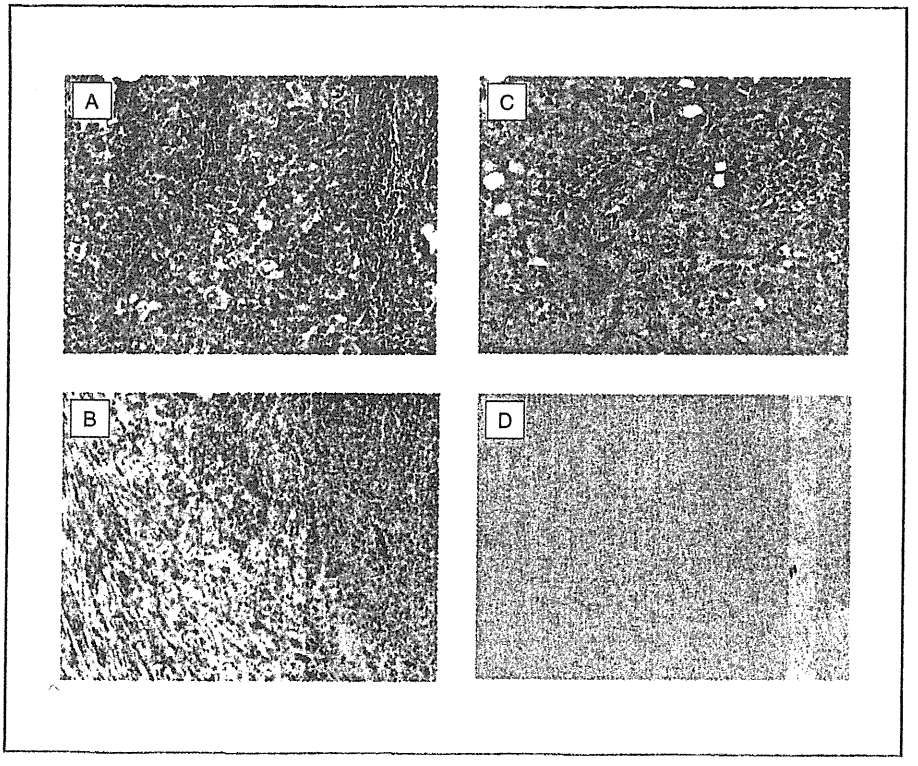

図 4　RFA 施行，非施行腫瘍の病理像

A：RFA 非施行腫瘍の H&E 染色像（× 400）
B：RFA 非施行腫瘍の NADH 染色像（× 400）
C：RFA 施行腫瘍の H&E 染色像（× 400）
D：RFA 施行腫瘍の NADH 染色像（× 400）

（カラーグラビア p2　写真 1 参照）

表2　病理組織学的結果

	症例数
組織型	
浸潤性乳管	43(88%)
浸潤性小葉	1(2%)
粘液	2(4%)
髄様	2(4%)
非浸潤性乳管	1(2%)
組織学的グレード	
1	22(45%)
2	16(33%)
3	11(22%)
リンパ節転移 (n)	
陰性	39(80%)
陽性	10(20%)
病理学的全腫瘍径 (cm)	
中央値	1.7
レンジ	0.1～8
extended intraductal component (EIC)	
あり	23(47%)
なし	26(53%)
RFA の病理組織学的効果判定	
変性径 / 長径 (cm)	
中央値	3.0
レンジ	0～6.6
変性径 / 短径 (cm)	
中央値	2.2
レンジ	0～6.6
不完全焼灼例	18(37%)
浸潤部遺残	7(14%)
非浸潤部遺残	11(23%)

宜，腫瘍の焼灼状態をモニタリングする。当院での RFA 治療時間の中央値は 8.7 分で，施術終了時には US 上，腫瘍影は発生したバブル陰影により観察不能となる（図 3）。このバブル像を US 上の熱変性範囲と想定し記録しておく。RFA 終了時のニードルの先進部と腫瘍中心部の温度も記録しておき，RF 目標温度に達しているかを記録しておく。

施術終了時に合併症の有無を確認し，予定されている乳房切除術を実施する。このとき，予定されていた手術が安全に実施できたかどうか，手術後の合併症，入院期間などに関しても記録しておく。切除標本はただちに病理組織検室にて nicotinamide adenine dinucleotide (NADH)-diphorase 染色用の凍結保存用検体が採取され，通常の H&E 染色および NADH 染色にて抗腫瘍効果の判定がなされた。

RFA 施行腫瘍と非施行腫瘍の H&E 染色および NADH 染色像を図 4 に示した。RFA 施行腫瘍では NADH 染色

表3　病理組織学的腫瘍径とRFAの成績

病理学的腫瘍径 (t)*	患者数	完全焼灼 (%)	不完全焼灼 (%)
≦2 cm	29	25(86%)	4(14%)
＞2 cm	20	6(30%)	14(70%)

＊：浸潤部，非浸潤部を含んだ全腫瘍径

表4　EICの有無とRFAの成績

	患者数	完全焼灼 (%)	不完全焼灼 (%)
EIC(＋)	23	9(39%)	14(61%)
EIC(－)	26	22(85%)	4(15%)

表5　RFA後腫瘍切除を伴う安全性試験の報告

報告者 (年)	患者数	腫瘍径 (T)	使用装置	Power (W)	治療時間・中央値 (分)	完全焼灼率 (%)	合併症
Jeffery ら[1] (1999)	5	T2-3	LeVeen	20～60	30	80	なし
Izzo ら[2] (2001)	26	T1-2	LeVeen	25～80	15	96	皮膚熱傷×1
Burak ら[3] (2003)	10	T1	LeVeen	-	13.8	90	なし
Singletary ら[4] (2003)	29	T1-2	RITA	-	-	86	皮膚熱傷×1
Hayashi ら[5] (2003)	22	T1	RITA	-	15	64	皮膚熱傷×1 創感染×4
Fornage ら[6] (2004)	20	T1	RITA	-	15	95	なし
Noguchi ら[7] (2006)	10	T1	RITA	-	15	100	なし
Khatri ら[8] (2007)	15	T1	Cool-Tip	7～36	21	93	皮膚変形×2 創感染×1
Medina-Franco ら[9] (2008)	25	T1-2	Elektrotorm	-	11	76	皮膚熱傷×3 創感染×1
Garbay ら[10] (2008)	10	IBTR, ≦3 cm	LeVeen	25～32	11	70	
Imoto ら[11] (2009)	30	T1	LeVeen	5～42	18	85	皮膚熱傷×2 大胸筋熱傷×7
present study	49	T1-2, ≦3 cm	Cool-Tip	5～118	8.7	63	皮膚熱傷×2 大胸筋熱傷×3

陰性で，細胞死が示唆された。NADH染色陰性標本のH&E染色での特徴は，①細胞核の淡明粗造化，線状化，濃縮，②間質の列隙形成，③無構造化した間質内の細胞が挙げられた。NADH染色とH&E染色を併用した細胞死判定により主腫瘍ばかりでなく離れた部位の娘結節や乳管内病変 (extended intraductal component：EIC) の効果判定も可能となった。

病理組織学的な結果を表2に示した。浸潤部と非浸潤部を合わせた病理学的全腫瘍径の中央値は1.7 cm（レンジ0.1～8 cm）でEICを認めた症例が23例（47％）であった。乳房でのCool-

tip システム（17G）での RFA 焼灼範囲は中央値で 3.0 × 2.2 cm であった。US 腫瘍径 3 cm 以下の全 49 例中，18 例（37 %）が不完全焼灼で 7 例（14 %）に浸潤部での非焼灼残存が確認された。US 腫瘍径 2 cm 以下の全 38 例中，10 例（26 %）が不完全焼灼で 6 例（16 %）に浸潤部での非焼灼残存が確認された。

一方，浸潤部，非浸潤部を含んだ病理学的全腫瘍径 2 cm 以下の症例では，29 例中 25 例（86 %）に完全焼灼が確認された（表 3）。さらには EIC の有無での治療成績は，EIC(－)26 例中，22 例（85 %）に完全焼灼が確認された（表 4）。当院での結果より，病理学的腫瘍径 2 cm 以下で EIC(－) の症例が RFA の良い適応となることが確認された。ただし，術前の画像診断で対象の絞り込みができるかどうかが鍵となる。

プライマリーエンドポイントである本手技の合併症は，皮膚熱傷が 2 例，大胸筋熱傷が 3 例でいずれも保存的に軽快，治癒しており，入院期間の延長なども認めていない。本試験により RFA 手技の安全性は確認されたものと考える。

海外での RFA 試験と今後

1999 年から今日までの RFA 後腫瘍切除試験の報告を表 5 にまとめた[1)-11)]。すべてが単施設からの報告で，適応やデバイスは異なり，完全焼灼率も 64 ～ 100 %である。症例数も少数であり保険収載の承認を獲得するための十分なエビデンスとなる報告は見当たらない[12)]。

乳癌に対するマイクロ波熱凝固療法

ラジオ波とマイクロ波はともに電磁波の一種であり，腫瘍の凝固能に関しては各々特徴があるが，治療に供される周波数はラジオ波が 460 kHz，マイクロ波が 2,450 MHz である。オープン MR システムを利用して使用する場合にはラジオ波は干渉し合うことになり，マイクロ波が使用可能となる。乳癌に対してはオープン MR システム下での肝転移に対する治療が報告されているが[13)]，原発巣に対しては少数例の報告にとどまっている。

おわりに

乳癌の低侵襲局所療法である RFA などの non surgical ablation 療法は正しい適応や手技のもとに実施されれば，従来の外科的切除に劣らない成績を残せるものと期待する。本邦では薬事法上承認されている RFA が一番の近道と考え，その評価を開始した。結論は，ターゲットにした腫瘍は安全に，完全に細胞死に至らせることが可能であることは確認されたが，乳房温存療法と同様に画像診断では検出できない乳管内病変の遺残が問題となる。引き続きデバイスや手技の開発，改善とともに本治療の中～長期的安全性，整容性，局所制御能を評価していく必要がある。エビデンスが不十分な現状では，十分なインフォームドコンセントと確立されたモニタリングシステムのもと，臨床試験としてのみ実施されるべき治療であると考える。

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Original Articles

Feasibility Study of Docetaxel with Cyclophosphamide as Adjuvant Chemotherapy for Japanese Breast Cancer Patients

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Objective: The 7-year follow-up of the US oncology 9735 trial demonstrated the superiority of TC [docetaxel (DTX)/cyclophosphamide (CPA)] to doxorubicin/CPA therapy. To introduce TC therapy in Japan, the verification of the safety and tolerability is essential. We performed a collaborative prospective safety study with Okayama University to introduce TC therapy.
Methods: The subjects were 53 patients aged from 33 to 67 years at intermediate risk based on the St Gallen risk classification who underwent radical surgery for primary breast cancer between August 2007 and December 2008. As post-operative adjuvant chemotherapy, four cycles of TC (DTX 75 mg/m^2 + CPA 600 mg/m^2) were administered at 3-week intervals. Adverse events were evaluated based on National Cancer Institute—Common Terminology Criteria for Adverse Events ver. 3.0. The safety and completion rate were evaluated as the primary and secondary endpoints, respectively.
Results: Regarding hematological toxicity, Grade (G) 4 neutropenia occurred in 71.7% and G3 in 26.4%. G3–4 leukopenia developed in 32.1% and 56.6%, respectively, G4 anemia in 1.9% and G1–2 anemia in 26.4%. Regarding non-hematological toxicity, systemic malaise, skin eruption, edema, myalgia, arthralgia and nausea were noted in most patients. The completion rate was 94.3%, dose reduction was necessary in 7.5% and granulocyte colony-stimulating factor (G-CSF) support was required in 17.0%. On comparison between patients aged 65 years or older and younger than 65 years, the completion rate, dose reduction and incidence of febrile neutropenia (FN) were higher in the elderly patients. G-CSF support was more often needed in this subgroup.
Conclusions: TC therapy is tolerable for Japanese patients, but attention should be paid to the development of FN and neutropenia. The completion rate was lower in the elderly patients, showing that tolerability was not necessarily favorable.

Key words: breast cancer – docetaxel – cyclophosphamide – adjuvant therapy – safety

INTRODUCTION

The standard regimen most widely adopted for post-operative adjuvant chemotherapy for breast cancer is combination chemotherapy with drugs including anthracycline. Taxanes are also key drugs of post-operative adjuvant chemotherapy for breast cancer, and the efficacy of taxanes administered in addition to anthracycline regimens has been demonstrated by many randomized control trials (RCTs) (3). The US oncology 9735 trial (USON9735) was the first RCT in which anthracycline and taxane were directly compared as post-operative adjuvant chemotherapies for breast cancer, and the analytical results of a 7-year median follow-up have been reported (1,2). AC [doxorubicin 60 mg/m^2 i.v. on day 1; cyclophosphamide (CPA) 600 mg/m^2 i.v. on day 1; every 21 days × 4 cycles] and TC [docetaxel (DTX) 75 mg/m^2 i.v. on day 1; CPA 600 mg/m^2 i.v. on day 1; every 21 days × 4 cycles] were compared as post-operative adjuvant chemotherapies for Stages I, II and III resectable invasive breast cancer. The primary endpoints were disease-free survival (DFS) and overall survival (OS). The lymph node metastasis

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