International Journal of Clinical Oncology (2019) 24:603–607
https://doi.org/10.1007/s10147-019-01423-z

INVITED REVIEW ARTICLE

RFA experiences, indications and clinical outcomes

Takayuki Kinoshita[1]

Received: 21 February 2019 / Accepted: 22 February 2019 / Published online: 11 March 2019

Abstract

Backgound Early-stage breast cancer is increasingly detected by screening mammography, and we aim to establish radiofrequency ablation therapy (RFA) as a minimally invasive, cost-efficient, and cosmetically acceptable local treatment. Although there were many studies on resection after RFA, none of them provided sufficient evidence to support RFA as a standard therapy for breast cancer.

Results In our Phase I study, localized tumors with a maximum diameter of 2 cm, preoperatively diagnosed by imaging and histopathology, were treated with RFA. A 90% complete ablation rate was confirmed histopathologically. Our phase II multicenter study of RFA without resection for early breast cancer will evaluate the long-term safety and efficacy of RFA as well as its cosmetic results, which are a perceived advantage of this technique. We started a phase III multicenter study to demonstrate the non-inferiority of RFA compared with standard treatment (breast-conserving surgery) in terms of ipsilateral breast tumor recurrence (IBTR) rate, which is the best index of local control.

Conclucion To standardize RFA for breast cancer, the results of our multicenter study, Radiofrequency Ablation Therapy for Early Breast Cancer as Local Therapy (the RAFAELO study) that began in 2013, are eagerly awaited.

Keywords Radiofrequency ablation therapy · Non-surgical ablation · Small breast carcinoma · Multi-center study

Introduction

In the surgical treatment of breast cancer, conservative treatment and sentinel lymph node biopsy have already become the standard of care. In addition to being less invasive, treatments are expected to have good esthetic outcomes. In Japan, the incidence of breast cancer and the detection rate for early-stage disease have increased due to widespread use of mammography and advances in diagnostic imaging, as is the case in other developed countries. Given this historical background, non-surgical ablative therapies, non-invasive surgical therapies, have started to attract attention due to patient demand. The non-surgical ablative therapies used in clinical practice for breast cancer are cryoablation, high-intensity focused ultrasound (HIFU), and radiofrequency ablation (RFA). In Japan, RFA became widespread quickly because of the prevalence and convenience of the device. Phase I and phase II multicenter clinical studies of RFA as treatment for early-stage breast cancer were started in 2006 under the Evaluation System of Investigational Medical Care. A prospective phase III study was started in 2013 under the Advanced Medical Service System.

Current status of RFA in Japan

In Japan, RFA is used for the treatment of liver cancer. During RFA, alternating electric currents change the ions in the tissue surrounding the electrodes and the heat generated as the result of friction from this change coagulates and necrotizes cancer cells. The Cool-tip FR System (Medtronic, Energy-Based Devices, Interventional Oncology, Boulder, CO, USA), which consists of a single needle and allows for easier heat control, is the configuration most commonly used at present for breast cancer. One advantage of this therapy is that this device has already been widely used for the treatment of liver cancer. Therefore, RFA is likely to be prevalent in Japan.

According to a survey conducted in the fiscal year 2010 by the Japanese Breast Cancer Society, RFA was used to treat breast cancer in 1049 patients at 29 institutions in Japan. However, indications, standard procedures, and

✉ Takayuki Kinoshita
takinosh@ncc.go.jp

[1] National Cancer Center Hospital, Tokyo, Japan

management systems varied. At many institutions, RFA was not used within the framework of clinical studies. In this situation, the Japanese Breast Cancer Society warned to use RFA for breast cancer as a part of clinical studies. Moreover, the Japanese Study Group for Minimally Invasive Treatment of Breast Cancer called for examination of the retrospective data obtained in the follow-up of patients and their quality of life. The results confirmed that outcomes for RFA and conservative treatment in Japan were similar for patients with early-stage breast cancer of 2 cm or less in diameter.

Overseas studies on RFA

Studies on resection after RFA published from 1999 to the present are summarized in Table 1 [1–13]. Although there were many studies, all were based at a single institution. The indications and devices used varied. The complete ablation rate ranged from 64 to 100%. The number of subjects in each study was small. None of these studies provided sufficient evidence to support RFA as a standard therapy.

Studies on non-invasive surgical treatment without subsequent resection

Studies on RFA without resection are summarized in Table 2 [14–16]. The number of subjects and duration of observation are both insufficient and the evidence supporting these therapies as new treatment methods is weak.

Another obstacle is that multiple steps are necessary to show equivalency with breast conservation surgery. Most data are from studies of ablation and resection, with strong

Table 1 Studies of RFA followed by surgical excision

Author (year)	No. of pts.	Disease (T)	Device	Power (W)	Median treatment time (min)	Complete ablation (%)	Complications
Jeffery et al. (1999) [1]	5	T2–3	LeVeen	20–60	30	80	None
Izzo et al. (2001) [2]	26	T1–2	LeVeen	25–80	15	96	Skin burn × 1
Burak et al. (2003) [3]	10	T1	LeVeen	–	13.8	90	None
Singlatary et al.(2003) [4]	29	T1–2	RITA	–	–	86	Skin burn × 1
Hayashi et al. (2003) [5]	22	T1	RITA	–	15	64	Skin burn × 1 Wound infection × 4
Fornage et al. (2004) [6]	20	T1	RITA	–	15	95	None
Noguchi et al. (2006) [7]	10	T1	RITA	–	15	100	None
Khatri et al. (2007) [8]	15	T1	Cool-Tip	7–36	21	93	Skin puckering × 2 Wound infection × 1
Medina-Franco et al. (2008) [9]	25	T1–2	Elektrotorm	–	11	76	Skin burn × 3 Wound infection × 1
Garbay et al. (2008) [10]	10	IBTR, ≤ 3 cm	LeVeen	25–32	11	70	N/A
Imoto et al. (2009) [11]	30	T1	LeVeen	5–42	18	85	Skin burn × 2 Muscle burn × 7
Kinoshita et al. (2011) [12]	49	T1–2, ≤ 3 cm T1	Cool-Tip	5–118	8.7	63 89	Skin burn × 2 Muscle burn × 3
Ohtani et al. (2011) [13]	41	T1	Cool-Tip	9	9	88	Skin burn × 2

Table 2 Studies of in situ ablation without surgical excision

Author (year)	Type of ablation	No. of pts.	Tumor size (cm)	Post-treatment assessment	Results
Oura et al. (2007) [14]	RFA	52	≤ 5	FNA, MRI	No local recurrences after median follow/up of 15 months
Yamamoto et al. (2011) [15]	RFA	29	Luminal A or DCIS, ≤ 1	VAB, MRI	No residual disease in 27/29 No local recurrences after median follow-up of 17 months
Ito et al. (2018) [16]	RFA	386	≤ 3.5	MRI, US	The IBTR-free survival rate at 5 years was 97%, 94%, 87% in pts, with a tumor size ≤ 1.0 cm, 1.1–2.0, and > 2.0 cm, respectively

data for RFA, but there is limited experience with ablation-only trials.

For RFA, the results of a large-scale Japanese multicenter clinical study, Radiofrequency Ablation Therapy for Early Breast Cancer as Local Therapy (the RAFAELO study) that began in 2013, are eagerly awaited.

Radiofrequency ablation therapy for early breast cancer as local therapy (the RAFAELO study)

The aim of the prospective study is to demonstrate that RFA can be an alternative treatment strategy for early-stage breast cancer to partial mastectomy. To demonstrate that the effectiveness and safety are equivalent between RFA and partial mastectomy, the end point of prospective study should be disease-free survival in ipsilateral breast and adverse events.

The study flow is described in Fig. 1. This prospective phase III study is planned as a single-arm study to compare with the results of previous randomized control study of lumpectomy or partial mastectomy. RFA is performed with sentinel lymph node biopsy followed by whole breast irradiation. The appropriate adjuvant medical therapy needs to be offered for all patients according to the guidelines. The vacuum-assisted breast biopsy is done at 3 months after whole breast irradiation. Partial mastectomy or total mastectomy is mandatory for the patients with residual tumor diagnosed by vacuum-assisted biopsy. Thereafter, the programed examinations including breast ultrasonography, mammography, and contrast breast MRI will be performed for every patient to diagnose the ipsilateral breast tumor recurrence, which is described particularly in Table 3.

The primary end point of this study is 5-year ipsilateral breast tumor recurrence-free survival rate.

The secondary end points of this study are overall survival, distant disease-free survival, adverse events of RFA, and tumor viability after RFA.

A small breast mass is suitable for RFA. Our data indicate that histologically complete tumor necrosis was significantly less frequent in tumors of more than 1.5 cm in diameter than those under 1.5 cm in diameter. Therefore, eligibility criteria were defined as a single breast mass under 1.5 cm in diameter by radiological findings. In addition, the clinically node negative was also defined as eligibility criteria. The assessment of complete ablation is performed at 3 months after finishing whole breast irradiation by ultrasonography-guided vacuum-assisted needle biopsy. The specimen obtained from two lesions among which one was in the center and the other in the peripheral area of the ablated lesion. Pathological diagnosis is done by both hematoxylin and eosin staining and nicotinamide adenine dinucleotide (NADH) diaphorase staining. The conditions of NADH-diaphorase staining were the same as previously described. In case tumor viability is confirmed, the participant has to undergo partial mastectomy as soon as possible. The rate of conversion to partial mastectomy is also recorded, and the participants who received partial mastectomy are included in the analysis of end points.

This study is a phase III, single-arm multicenter study being conducted with the participation of 11 hospitals in Japan. In our experimental therapy, a radiofrequency electrode needle is inserted through the skin into the breast lesion under imaging guidance, followed by thermal ablation with radiofrequency waves. RFA will be conducted under general anesthesia. The Cool-tip™ RF Ablation Single Electrode Kit (Medtronic, CO, USA) will be used to standardize the evaluation of the ablation effect. After RFA, all patients will receive radiotherapy and

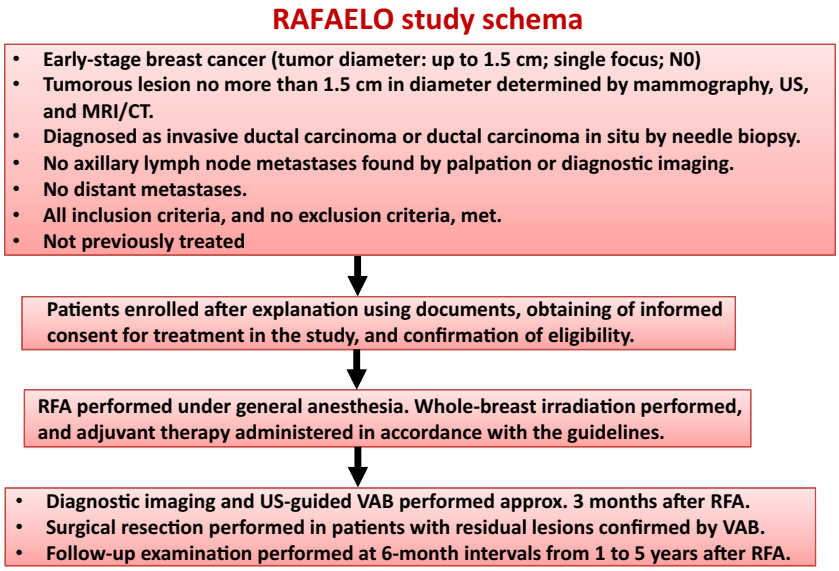

Fig. 1 RAFAELO study schema. This prospective phase III study is planned as a single-arm study to compare with the results of previous randomized control study of lumpectomy or partial mastectomy

Table 3 Schedule of follow-up after RFA of RAFAELO study

Postoperative period	Pre-	Intra and post	Within 1 week	*	12 months	18 months	2 years	2.5 years	3 years	3.5 years	4 years	4.5 years	5 years
Patients' background: Current and previous medical history	○												
Interview	○		○	○	○	○	○	○	○	○	○	○	○
Clinical examination	○	○		○	○	○	○	○	○	○	○	○	○
MMG	○				○		○		○		○		○
Needle biopsy (CNB/VAB/ MMT)	○			○									
Breast US	○	○		○	○	○	○	○	○	○	○	○	○
Breast MRI and / or CT	○			○	○		○		○		○		○
CXP	○				○		○		○		○		○
Tumor markers	○			○	○	○	○	○	○	○	○	○	○
Photograph-based evaluation of esthetic outcome													
Questionnaire-based assessment													

*3 months after RT

systemic therapy according to the ER, HER2, tumor grade, and lymph node status of the primary tumor. Residual lesions after RFA will be assessed approximately 3 months after radiotherapy using imaging and pathological studies. All patients will undergo vacuum-assisted biopsy regardless of the imaging results. If specimens show viable tumor tissue, additional excision will be performed. Follow-up evaluation for residual tumor, including clinical breast examination and diagnostic imaging (ultrasound, MRI, and mammography), will be performed yearly after RFA. This trial has been registered at the UMIN Clinical Trials Registry as UMIN000008675. The trial was activated in August 2013, with a total of 372 patients enrolled by the end of November 2017.

Conclusion

We expect that non-surgical ablative therapies including RFA, which are used as minimally invasive local therapies for breast cancer, can achieve outcomes equivalent to surgical resection if the right procedure is carried out for the right indication. Data on non-surgical ablative therapies including RFA, cryoablation, and HIFU are steadily accumulating. We believe that these therapies can replace lumpectomy, the standard treatment for breast cancer, in the near future.

These studies were supported in part by a Grant for Project Promoting Clinical Trials for Developing of New Drugs and Medical Devices from the Japan Agency for Medical Research and Development (AMED).

Compliance with ethical standards

Conflict of interest The author has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

References

1. Jeffrey SS et al (1999) Radiofrequency ablation of breast cancer. Arch Surg 134:1064–1068
2. Izzo F et al. Radiofrequency ablation in patients with primary breast carcinoma Cancer 2001;92: 2036–2044
3. Burak WE et al (2003) Radiofrequency ablation of invasive breast carcinoma followed by delayed surgical resection. Cancer 98:1369–1376
4. Singletary SE et al (2003) Radiofrequency ablation for primary breast cancer. Breast Cancer 10:4–9
5. Hayashi AH et al (2003) Treatment of invasive breast carcinoma with ultrasound-guided radiofrequency ablation. Am J Surg 185:429–435
6. Fornage BD et al (2004) Small breast cancer treated with US-guided radiofrequency ablation: feasibility study. Radiology 231:215–224

7. Noguchi M et al (2006) Radiofrequency ablation of small breast cancer followed by surgical resection. J Surg Oncol 93:120–128
8. Khatri VP et al (2007) A phase II trial of image-guided radiofrequency ablation of small invasive breast carcinoma: use of saline-cooled tip electrode. Ann Surg Oncol 14:1644–1652
9. Medina-Franco H et al (2008) Radiofrequency ablation of invasive breast carcinoma: a phase II trial. Ann Surg Oncol 15:1689–1695
10. Garbay JR et al (2008) Radiofrequency thermal ablation of breast cancer local recurrence: a phase II clinical trial. Ann Surg Oncol 15:3222–3226
11. Imoto S et al (2009) Feasibility study on radiofrequency ablation followed by partial mastectomy fot stage I breast cancer patients. Breast 18:130–134
12. Kinoshita T et al (2011) Radiofrequency ablation sa local therapy for early breast carcinomas. Breast Cancer 18:10–17
13. Ohtani S et al (2011) Radiofrequency ablation of early breast cancer followed by delayed surgical resection. A promising alternative to breast-conserving therapy. Breast 20(5):431–436
14. Oura S, Tamaki T, Hirai I et al (2007) Radiofrequency ablation therapy in patients with breast cancers two centimeters or less in size. Breast Cancer 14:48–54
15. Yamamoto N, Fujimoto H, Nakamura R et al (2011) Pilot study of radiofrequency ablation therapy without surgical excision for T1 breast cancer. Breast Cancer 18:3–9
16. Ito T, Oura S, Nagamine S et al (2018) Radiofrequency ablation of breast cancer: a retrospective study. Clin Breast Cancer 18:495–500