Non-surgical therapy and radiologic assessment of stage I breast cancer treatment with novel enzyme-targeting radiosensitization: Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, type II (KORTUC II)

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Abstract. The new enzyme-targeting radiosensitization treatment, Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, type II (KORTUC II), markedly enhances the radiotherapeutic effect of treatment for various types of locally advanced malignant neoplasms. Patients who had declined surgical treatment and systemic chemotherapy, as well as a total of 14 stage I breast cancer patients, were enrolled. A maximum of 6 ml of KORTUC II was injected into tumor tissue twice a week under ultrasonographic guidance, immediately prior to each administration of radiation therapy. The median observation period was 21.6 months with a range of 4-48 months, and the therapy was well tolerated. Contrast-enhanced magnetic resonance imaging and [^{18}F]-fluorodeoxyglucose positron emission computed tomography revealed that all primary breast tumors completely responded, and none of the subjects experienced local recurrence during the observation period. Ultrasonography depicted tumor-like findings in 2/14 cases after therapy. The intratumoral flow signal on color-Doppler sonography was positive in 4/14 cases before therapy, and the signal disappeared from all cases after therapy. The absence of a flow signal after therapy suggested that the tumor-like findings on ultrasonography were from scar tissue. Excellent local control based on accurate radiological evaluation implies that KORTUC II has the potential to replace surgery as a therapeutic option for stage I breast cancer. Precise evaluation by various radiological modalities helped to gage the success of this therapy.

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Introduction

Breast conserving surgery has become the most popular surgical procedure for primary breast cancer (1). The significance of extended resection has become less important, since the long-term survival rate among women who undergo breast-conserving surgery is the same as that among women who undergo radical mastectomy (2). Thus, nowadays, local control is expected to be minimally invasive on the basis that permanent curability is estimated to be comparable. Various types of non-surgical ablation have been introduced as a local control for early breast cancer that also achieve cosmetic gains (3-7). A new enzyme-targeting radiosensitization treatment containing hydrogen peroxide and sodium hyaluronate for percutaneous injection, Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, type II (KORTUC II) (8), was recently developed. It markedly enhances the radiotherapeutic effect of treatment for various types of tumors that are not superficially exposed, such as breast cancer and other types of soft tissue tumors (8). As precise assessment of therapeutic efficacy by radiological imaging is essential for the success of KORTUC II, contrast enhanced breast magnetic resonance imaging (CE-breast MRI), ultrasonography (US) and [^{18}F]-fluorodeoxyglucose positron emission computed tomography (FDG-PET-CT) were employed to assess therapeutic outcomes. The aim of the present study was to report the therapeutic outcome of KORTUC II for stage I breast cancer precisely assessed by the aforementioned radiological imaging modalities.

Materials and methods

KORTUC II radiosensitizer was used as a percutaneous injection for breast cancer as approved by our local ethics committee. Since hydrogen peroxide is an irritant and may cause severe adverse effects, experimental studies were performed prior to clinical applications in order to ascertain safety of the method (9). In order to allow long-acting radiosensitization of the local tumor tissue, sodium hyaluronate was added to hydrogen peroxide in order to make the solution more viscous and to slow the degradation of the hydrogen peroxide (9).

Table I. Summary of the subject data.

Case	Observation period (months)	Age (years)	Assessed by MRI[a]	Assessed by US[b]	Flow signal on color-Doppler US[c]	PS artifact on US[d]
1	29	67	CR→CR	CR→CR	N→N	N→N
2	48	77	CR→CR	CR→CR	P→N	N→N
3	38	79	CR→CR	27.3→45.5	P→N	N→N
4	38	76	CR→CR	CR→CR	P→N	N→N
5	32	71	CR→CR	CR→CR	N→N	N→N
6	20	74	CR→CR	CR→CR	N→N	N→N
7	19	79	CR→CR	CR→CR	N→N	N→N
8	16	89	CR→CR	CR→CR	N→N	N→N
9	16	64	CR→CR	53.8→CR	P→N	N→N
10	13	43	CR→CR	CR→CR	N→N	N→N
11	11	62	CR→CR	CR→CR	N→N	N→N
12	11	61	CR→CR	CR→CR	N→N	N→N
13	7	78	CR→NA	CR→CR	N→N	N→N
14	4	51	CR→NA	CR→NA	N→N	N→N

PS, posterior shadow; CR, complete response; NA, not assessed; P, positive; N, negative. [a]Tumor response of the primary tumor assessed by contrast enhanced breast magnetic resonance imaging (CE-breast MRI) (immediately after the completion of therapy → final examination). The outcomes of CE-breast MRI and [^{18}F]-fluorodeoxyglucose positron emission computed tomography were identical. [b]Reduction rate (%) of the primary tumor assessed by ultrasonography (US) (immediately after the completion of therapy → final examination). [c]Change in flow signal on color-Doppler US (before therapy → after the completion of therapy). [d]Change in posterior shadow artifact from the primary tumor on US (before therapy → after the completion of therapy).

Preparation of the radiosensitizing agent. The radiosensitizing agent was composed of 0.83% sodium hyaluronate and 0.5% hydrogen peroxide, and was prepared by adding 0.5 ml of 3% hydrogen peroxide solution (Oxydol; Ken-ei Pharmaceutical Co. Ltd., Osaka, Japan) to a commercially available disposable syringe containing 2.5 ml of 1.0% sodium hyaluronate. Hydrogen peroxide was added immediately before use in order to avoid degradation of the sodium hyaluronate due to oxidation by hydrogen peroxide.

Patient selection and radiotherapy. Fourteen female stage I (10) breast cancer patients (invasive ductal carcinomas) were enrolled in the KORTUC II trial. Each patient signed an informed consent form before participation in the study. Patient data are summarized in Table I. Patients were eligible for the study if they had stage I breast cancer and had either contraindications to general anesthesia due to significant comorbidity or had declined surgical and systemic chemotherapy treatment.

For each patient, radiation therapy with high-energy X-ray was delivered with an EXL-20TP linear accelerator equipped with a multi-leaf collimator (Mitsubishi Electric Co. Ltd., Tokyo, Japan) at an appropriate energy level (4 MV). Hypofraction radiotherapy was administered using a tangential field approach; the total dose was 44 Gy administered as a 2.75 Gy/fraction. Radiation therapy was performed five times a week for each patient. After the initiation of radiotherapy, an intratumoral injection of KORTUC II was performed under ultrasonographic guidance twice a week for 2 weeks, immediately prior to radiation therapy. A maximum of 6 ml of the agent was injected at each session. Cone-down boost irradiation was then delivered using an electron beam of appropriate energy for each individual patient, and was administered concurrently with a dose of 9 Gy in three fractions in the last week of radiotherapy.

A risk category was assigned to each patient according to the St. Gallen guidelines based on clinical tumor size and the pathological results of a core needle biopsy taken before therapy (11). Adjuvant systemic chemotherapy was not administered to any patients: 12 of 14 patients were classified as low risk and, according to the St. Gallen guidelines, chemotherapy is not recommended for low-risk patients (11). However, 1 of the 2 subjects with intermediate risk (case 12 in Table I), for whom the St. Gallen guidelines recommend the use of chemotherapy, declined systemic chemotherapy with their fully informed consent (11). Another St. Gallen intermediate-risk patient was too old to receive systemic chemotherapy (case 2 in Table I).

Endocrine therapy. All patients with breast tumors positive for hormonal receptor received endocrine therapy immediately after the completion of radiotherapy. Tamoxifen (40 mg/day per os) or an aromatase inhibitor (anastrozole 1 mg/day or exemestane 25 mg/day per os) was used for pre-menopausal and post-menopausal patients, respectively. Endocrine therapy was scheduled to continue for 5 years in all eligible patients.

Patient assessment (primary breast tumor and toxicity of therapy). Tumor response was assessed according to the RECIST criteria (12) using CE-breast MRI, FDG-PET-CT and US. Patients were assigned a toxicity grade from a

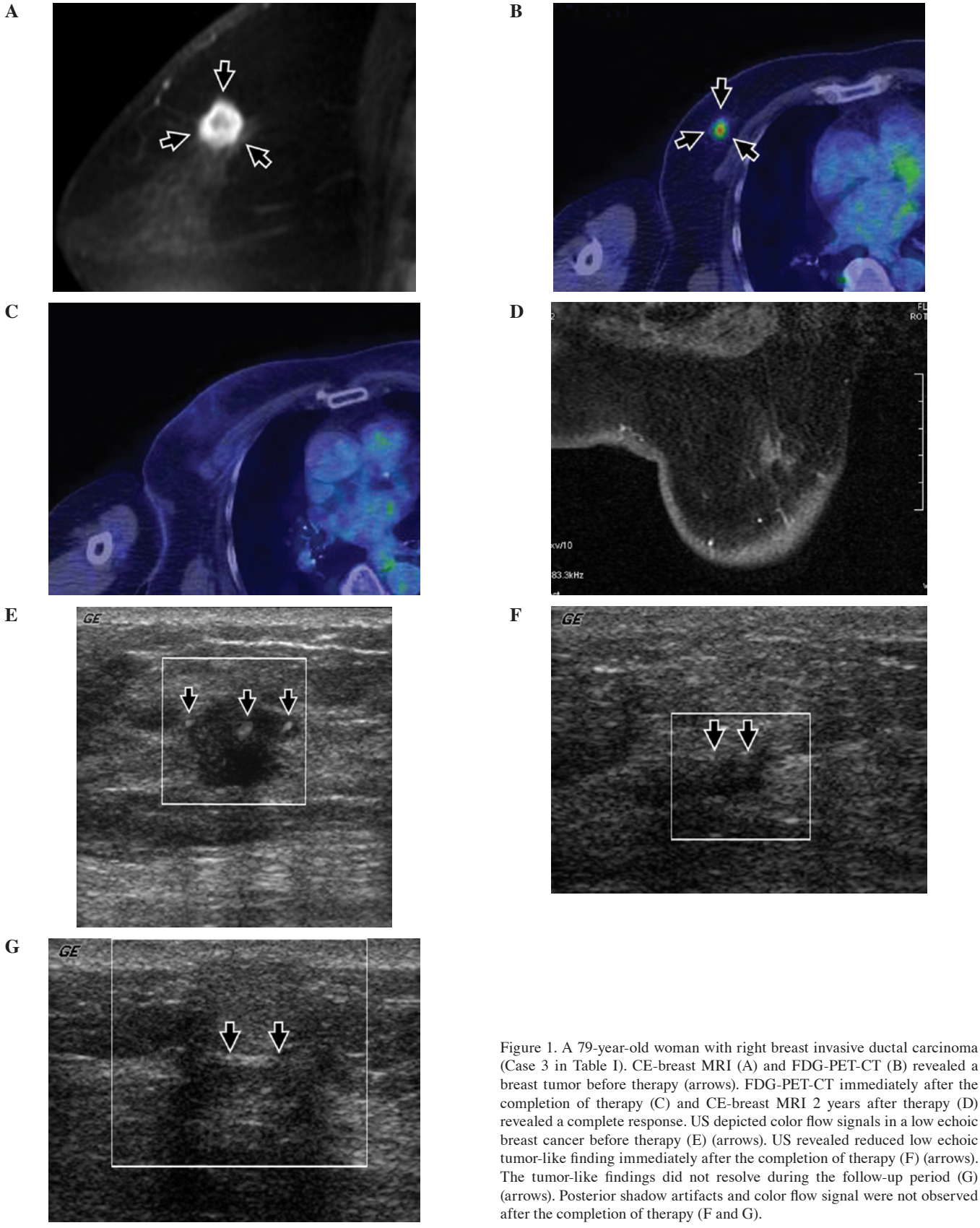

Figure 1. A 79-year-old woman with right breast invasive ductal carcinoma (Case 3 in Table I). CE-breast MRI (A) and FDG-PET-CT (B) revealed a breast tumor before therapy (arrows). FDG-PET-CT immediately after the completion of therapy (C) and CE-breast MRI 2 years after therapy (D) revealed a complete response. US depicted color flow signals in a low echoic breast cancer before therapy (E) (arrows). US revealed reduced low echoic tumor-like finding immediately after the completion of therapy (F) (arrows). The tumor-like findings did not resolve during the follow-up period (G) (arrows). Posterior shadow artifacts and color flow signal were not observed after the completion of therapy (F and G).

standard assessment scale (NIH common toxicity criteria). Treatment-related complications were assessed in detail in order to evaluate the feasibility of this approach. Posterior shadow artifacts from each tumor on US and flow signal on color-Doppler US were also assessed.

Each breast mass was scanned using a US unit (LOGIQ700MR; GE Healthcare, Milwaukee, WI, USA) with a 7-11 MHz linear-array transducer. CE-breast MRI was performed at 3.0 T (Signa EXCITE HDx; GE Healthcare) with subjects in the prone position. Dynamic MRI using a three-

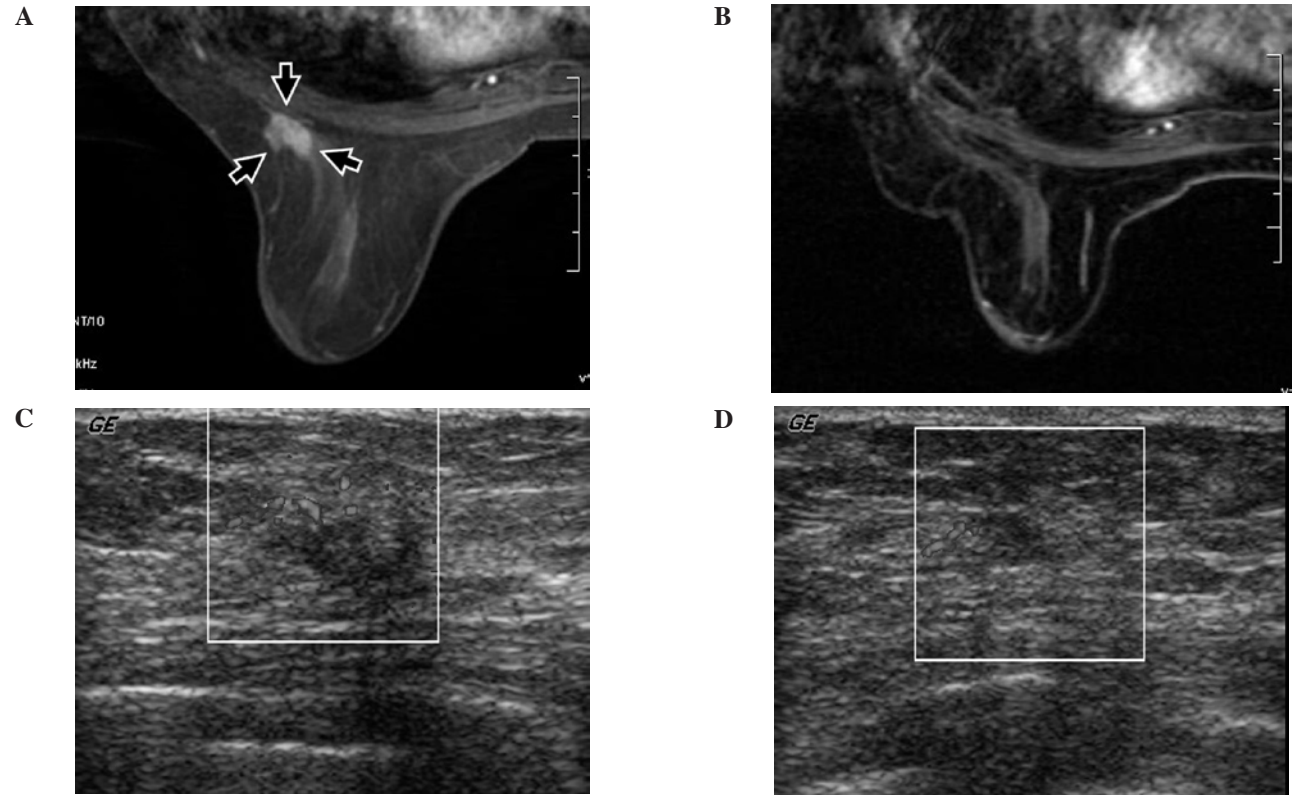

Figure 2. A 74-year-old woman with left breast invasive ductal carcinoma (case 6 in Table I). CE-breast MRI before therapy (A) revealed tumor enhancement (arrows). CE-breast MRI immediately after therapy (B) verified complete response of the lesion. US of the lesion before therapy (C) compared to immediately after therapy (D) also showed complete response of the lesion.

dimensional fast spoiled gradient-echo sequence (VIBRANT, volume imaging for breast imaging; TR 7.0 msec; TE 4.0 msec; flip angle 10˚; FOV 36x36 cm; matrix 512x256; slice thickness 3 mm; increment 0 mm; NEX 0.7) was obtained before and 8 times after (every 30 sec) a bolus injection of 0.1 mmol/kg gadolinium-diethylenetriamine pentaacetic acid at a rate of 3 ml/sec. Whole-body FDG-PET-CT scans were obtained on a Discovery ST Elite PET-CT system (GE Healthcare) consisting of a full ring dedicated PET and a 16-slice spiral CT. All patients were instructed to fast for 6 h before receiving an intravenous application of 3.5 MBq/kg FDG. Imaging was initiated ~60 min after the application of FDG. CT was acquired before PET with 50 mA/sec at 130 kV without administration of a non-ionic contrast agent. All images were reconstructed with a 5-mm slice thickness and a 3.7-mm increment. After CT, a 3-D mode PET was performed. The PET emission time per bed position was adapted to the patient body weight: <65 kg, 2 min per bed position; 65-85 kg, 2.5 min; and >85 kg, 3 min. Any focally elevated PET signal above normal that could be mapped to a tumor location was rated as positive for viable breast cancer (13). The interpreters of US (K.K.), CE-breast MRI (Y.M.) and FDG-PET-CT (J.H.) were provided information regarding tumor location, but were otherwise blinded to patient and therapy information.

Beginning and frequency of observation. Assessment of the primary tumor started within 2-4 weeks of the completion of radiotherapy, regardless of the endocrine therapy. CE-breast MRI and FDG-PET-CT were performed at least once a year following the completion of radiotherapy. US and a clinical examination were performed every 3 months. The mean observation period was 21.6 months with a range of 4-48 months.

Results

Adverse events. All patients experienced mild local pain at the injection site. For all 14 patients, radiation-induced dermatitis was mild (grade I) and equivalent to dermatitis induced after radiation therapy alone as described previously (8).

Assessment of primary breast tumors by CE-breast MRI and FDG-PET-CT. Patient data are summarized in Table I. All patients were unable or unwilling to undergo surgery, and therefore underwent non-surgical breast conservation therapy. All achieved a complete response (CR) (Figs. 1 and 2). At the completion of the follow-up period, none of the patients exhibited local recurrence. The findings of CE-breast MRI did not differ from those of FDG-PET-CT.

Assessment of primary breast tumors by US. US depicted tumor-like findings in 2 of 14 patients immediately after the completion of therapy (Fig. 1). CR was noted in 12 cases, partial response (PR) in 1 case and stable disease (SD) in 1 case. One of the tumor-like findings had disappeared by the end of follow-up (case 9 in Table I). Another tumor-like finding remained throughout the follow-up period (case 3 in Table I). No posterior shadow artifacts appeared in any of the patients throughout the observation period. Color Doppler-US

depicted an intratumoral flow signal in 4 of 14 tumors prior to therapy. This flow signal disappeared from all patients after the completion of therapy (Fig. 1). Absence of a flow signal continued during the observation period.

Discussion

Breast cancer surgery has changed dramatically over the past two decades. With the emergence of breast conserving therapy, many breast cancer patients now have the option of preserving a cosmetically acceptable breast without sacrificing survival. In 1984, Dr William Halsted published a landmark paper describing the outcome of the Halsted Radical Mastectomy (14). This procedure achieved improved survival, and thus the Halsted Radical Mastectomy became the standard care in breast cancer treatment. While survival from breast cancer improved with the Halsted Radical Mastectomy, it was clear that there was increased morbidity associated with this technique.

In the mid-1970s, the National Study of the Adjuvant Breast and Bowel Project (NSABP) published the results of the B-04 study, which demonstrated that there was no difference in survival between a radical mastectomy vs. a modified radical mastectomy, where the pectoralis muscles are preserved (15). Once the results of the NSABP B-04 landmark trial were reported, the surgical management of breast cancer moved in a more conservative direction.

In the mid-1980s, the NSABP B-06 trial demonstrated no difference in survival between mastectomy vs. lumpectomy followed by radiation (16). Recently, breast conserving surgery has become the most common surgical procedure for breast cancer (1). However, breast conserving surgery often degrades the cosmetic outcome to some degree. Therefore, various types of minimally invasive options have been employed as alternatives to surgical therapy, such as radiofrequency ablation (RFA) (5,6), focused ultrasound ablation (FUS) (3,4) and cryotherapy (7). These minimally invasive approaches are currently being investigated. Although they obtain excellent locoregional control (3-7), long-term control rates are unknown. Moreover, RFA and cryotherapy demand insertion of a moderately large needle into the breast (5-7). General anesthesia is essential to carring out RFA (5,6), MRI scanners to monitor the thermal distribution of FUS may be prohibitively expensive (3,4), and FUS takes too much time (3,4). It is also important to note that these non-surgical approaches to therapy require adjuvant radiation to non-ablated tissue in order to exterminate residual cancerous tissue (3-7). KORTUC II, radiation therapy intensified with radiosensitizer, is a logical technique for the ablation of micro-cancerous nests in the whole breast. KORTUC II has an advantage over other non-surgical ablation therapies, as it treats the whole breast at once. General anesthesia, insertion of a large needle and expensive equipment to monitor thermal distribution are unnecessary with KORTUC II.

Currently, most radiation therapy for breast cancer is performed using X-rays or high-energy electron beams from a linear accelerator (17,18). However, these forms of low-linear energy transfer (LET) radiation are not ideal for radiation therapy when compared to high-LET radiation. To overcome the disadvantages of these low-LET beams, KORTUC II, a new radiosensitizer containing hydrogen peroxide and sodium hyaluronate for injection into the tumor, was developed. Theoretically, KORTUC II inactivates anti-oxidative enzymes, produces oxygen in tumor tissue and converts a radioresistant tumor into a radiosensitive one. The favorable efficacy of KORTUC II has been reported *in vivo* and in preliminary clinical trials (8,9,19-22). The favorable therapeutic efficacy for stage I breast cancer in the present study suggests that KORTUC II is a powerful non-surgical therapeutic option for the treatment of stage I breast cancer. In the late 1960s and early 1970s, several studies investigated the use of hydrogen peroxide in radiotherapy, but this line of investigation appears to have been discontinued (23,24). In the present study, sodium hyaluronate, ordinarily used for intra-articular injection in chronic knee joint disorders, was combined with hydrogen peroxide in order to preserve oxygen concentration in tumor tissue for >24 h, and intratumoral injections of hydrogen peroxide alone resulted in a rapid lowering of oxygen concentration (unpublished data). The success of the present study may provide a reason to renew investigations into the use of hydrogen peroxide as a radiosensitizer.

Furthermore, worldwide advances in systemic therapy for breast cancer are compatible with KORTUC II. Adjuvant endocrine therapy, such as tamoxifen and aromatase inhibitors, increases the survival rate and is an acceptable option when patients have hormone receptor-positive breast cancer (25). The St. Gallen guidelines recommend adjuvant endocrine therapy alone to low-risk patients (11), a group to which almost all of the patients in our study population belonged. However, 2 patients in this study were rated as intermediate risk, for which the St. Gallen guidelines recommend administration of systemic adjuvant chemotherapy (11). One of the intermediate risk patients in the present study was too old for systemic chemotherapy and the other patient, though suitable for systemic chemotherapy, refused it. Although, systemic adjuvant chemotherapy prevents cancer recurrence and improves survival (17,18,26,27), patient preference for adjuvant therapy could feasibly eliminate the use of systemic chemotherapy (28). Patient preference may become the determinant for whether or not systemic chemotherapy is appropriate for intermediate risk stage I breast cancer patients, because of the balance between significant toxicities and benefit (11).

Precise assessment of therapeutic efficacy is important to gage the outcome of clinical trials. CE-breast MRI obtains over 95% sensitivity in the detection of breast cancer through enhancement of the lesion with gadolinium-based contrast material (29,30), and accurately reveals the tumor extent regardless of prior neoadjuvant chemotherapy (31-33). US has been reported to be more reliable for the detection and measurement of breast tumors than mammography, particularly in case of dense breast tissue (34-36). FDG-PET-CT is a reliable modality for the detection of primary breast tumors (37,38). Therefore, this study employed MRI, FDG-PET-CT and US as diagnostic tools for the precise assessment of the therapeutic effects of KORTUC II for primary breast tumors. US depicted tumor-like findings in 2 cases of CR as detected by CE-breast MRI and FDG-PET-CT. To the best of our knowledge, the diagnostic ability of FDG-PET-CT and US to detect primary breast tumors has not been compared. However, CE-breast MRI obtains equivalent to superior detection rates for bulky breast mass compared to US (36,39,40). Moreover, CE-breast MRI has been reported to have higher sensitivity in the detection of

small lesions (including intraductal spread) compared to US (39,40). Therefore, based on these US and MRI characteristics, the tumor-like US findings after therapy were probably scar tissue. Fibrous tissue in scar tissue develops after exposure to radiation (41,42) and causes ultrasound attenuation and a posterior shadow artifact (43). However, none of the patients in the present study had posterior shadow artifacts either before or after therapy, leading to the conclusion that these stage I breast tumors and scars resulting from KORTUC II therapy were too small to produce these types of artifacts. In addition, the absence of a flow signal on the color Doppler-US after therapy supports the possibility that the tumor-like findings are scar tissue (44). The present results suggest that tumor-like findings on US after therapy do not necessarily indicate tumor recurrence. Consequently, a CR on CE-breast MRI and on FDG-PET-CT was considered to be a reliable indicator of treatment efficacy.

In conclusion, based on these successful therapeutic outcomes, KORTUC II has a strong potential as a non-surgical therapy approach for stage I breast cancer. Radiological imaging modalities, including CE-breast MRI, US and FDG-PET-CT, can be used to monitor therapeutic effects, and the combination of these modalities is recommended to determine the success of this therapy. However, further investigation is required to confirm the long-term outcome of this new approach to stage I breast cancer therapy.

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