Evaluation of Changes in Tumor Shadows and Microcalcifications on Mammography Following KORTUC II, a New Radiosensitization Treatment without any Surgical Procedure for Elderly Patients with Stage I and II Breast Cancer

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Abstract: We introduced non-surgical therapy with a novel enzyme-targeting radiosensitization treatment, Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, Type II (KORTUC II) into early stages breast cancer treatment. The purpose of this study was to examine changes in tumor shadows and microcalcifications on mammography (MMG) following KORTUC II for elderly patients with breast cancer. We also sought to determine whether MMG was useful in evaluating the therapeutic effect of KORTUC II. In addition to MMG, positron emission tomography-computed tomography (PET-CT) was performed to detect both metastasis and local recurrence. In all 10 patients,
tumor shadows on MMG completely disappeared in several months following the KORTUC II treatment. The concomitant microcalcifications also disappeared or markedly decreased in number. Disappearance of the tumors was also confirmed by the profile curve of tumor density on MMG following KORTUC II treatment; density fell and eventually approached that of the peripheral mammary tissue. These 10 patients have so far have also shown neither local recurrence nor distant metastasis on PET-CT with a mean follow-up period of approximately 27 months at the end of September, 2010. We conclude that breast-conservation treatment using KORTUC II, followed by aromatase inhibitor, is a promising therapeutic method for elderly patients with breast cancer, in terms of avoiding any surgical procedure. Moreover, MMG is considered to be useful for evaluating the efficacy of KORTUC II.

**Keywords:** mammography; breast cancer; KORTUC; hydrogen peroxide; radiosensitizer; sodium hyaluronate

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1. **Introduction**

In recent years, local therapeutic procedures for breast cancer have been expected to be minimally invasive on the basis that permanent curability is estimated to be comparable to that of wider resections. Therefore, we introduced non-surgical therapy with a novel enzyme-targeting radiosensitization treatment, Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, Type II (KORTUC II) [1] into early stages breast cancer treatment. Using KORTUC II, low linear energy transfer (LET)-radioresistant tumors can be converted into radiosensitive ones; this has been already demonstrated based on both our experimental results which showed hydrogen peroxide to be a strong radiosensitizer [2-5] and our clinical studies [1,6-9].

The purpose of this study was to examine changes in tumor shadows and microcalcifications on mammography (MMG) following KORTUC II for elderly patients with breast cancer. We also sought to determine whether MMG was useful in evaluating the therapeutic effect of KORTUC II. In addition to MMG, positron emission tomography-computed tomography (PET-CT) was performed to detect both metastasis and local recurrence.

2. **Results**

Patient data are summarized in Table 1. In all 10 patients, tumor shadows on MMG completely disappeared in several months following the KORTUC II treatment. The concomitant microcalcifications also disappeared or markedly decreased in number. These data are shown in Tables 2 and 3.

Disappearance of the tumors was also confirmed by the profile curve of tumor density on MMG following the KORTUC II treatment; density fell and eventually approached that of the peripheral mammary tissue. The examples of changes in size of tumor shadows and microcalcifications are shown in Figures 1, 2, and 3.
These 10 patients have so far shown neither local recurrence nor distant metastasis also on PET-CT with a mean follow-up period of approximately 27 months at the end of September, 2010.

Table 1. Therapeutic effect of the radiosensitization treatment (KORTUC II) for breast cancer.

| Case | Diseased site | TNM class | Age/gender | Therapeutic effect | Side effects |
|------|--------------|-----------|------------|--------------------|--------------|
| 1    | right        | cT2N0M0   | 88F        | CR, NED>39 months  | mild skin burn |
| 2    | left         | cT2N0M0   | 79F        | CR, NED>38 months  | mild skin burn |
| 3    | right        | cT1cN0M0  | 79F        | CR, NED>38 months  | mild skin burn |
| 4    | left         | cT2N0M0   | 59F        | CR, NED>38 months  | mild skin burn |
| 5    | left         | cT1cN0M0  | 73F        | CR, NED>30 months  | mild skin burn |
| 6    | left         | cT2N0M0   | 79F        | CR, NED>20 months  | mild skin burn |
| 7    | right        | cT1cN0M0  | 77F        | CR, NED>20 months  | mild skin burn |
| 8    | right        | cT2N0M0   | 82F        | CR, NED>19 months  | mild skin burn |
| 9    | left         | cT2N0M0   | 63F        | CR, NED>15 months  | mild skin burn |
| 10   | right        | cT1cN0M0  | 77F        | CR, NED>38 months  | mild skin burn |

Table 2. Changes of tumor shadows following the radiosensitization treatment (KORTUC II).

| Case | Diseased site | TNM class | Age/gender | Therapeutic effect | Side effects |
|------|--------------|-----------|------------|--------------------|--------------|
| 1    | right        | cT2N0M0   | 88F        | CR, NED>39 months  | mild skin burn |
| 2    | left         | cT2N0M0   | 79F        | CR, NED>38 months  | mild skin burn |
| 3    | right        | cT1cN0M0  | 79F        | CR, NED>38 months  | mild skin burn |
| 4    | left         | cT2N0M0   | 59F        | CR, NED>38 months  | mild skin burn |
| 5    | left         | cT1cN0M0  | 73F        | CR, NED>30 months  | mild skin burn |
| 6    | left         | cT2N0M0   | 79F        | CR, NED>20 months  | mild skin burn |
| 7    | right        | cT1cN0M0  | 77F        | CR, NED>20 months  | mild skin burn |
| 8    | right        | cT2N0M0   | 82F        | CR, NED>19 months  | mild skin burn |
| 9    | left         | cT2N0M0   | 63F        | CR, NED>15 months  | mild skin burn |
| 10   | right        | cT1cN0M0  | 77F        | CR, NED>38 months  | mild skin burn |
### Table 2. Cont.

| Case | Pretreatment | After 3 mo. | After 12 mo. |
|------|--------------|-------------|--------------|
| 8    | Pretreatment | After 4.3 mo. | After 15.3 mo. |
|      | Shape is oval | Shape is irregular |
|      | Border is spiculated | Border is microlobulated |
|      | High density tumor | Equal density (fat-containing) |
|      | Spiculated core disappeared | Disappearance |
|      | Size is unchanged | |
| 9    | Pretreatment | After 3 mo. | After 14 mo. | After 18.6~33.4 mo. |
|      | Shape is oval | Shape is irregular |
|      | Border is spiculated | Border is microlobulated |
|      | High density tumor | Equal density (fat-containing) |
|      | Spiculated core disappeared | Disappearance |
| 10   | Pretreatment | After 3 mo. | After 14 mo. | After 18.6~33.4 mo. |
|      | Focal asymmetric density (FAD) | Unchanged from last time |

### Table 3. Changes of microcalcification following the radiosensitization treatment (KORTUC II).

| Case | Pretreatment | Time |
|------|--------------|------|
| 1    | Pretreatment | After 3.8 mo. | After 8 mo. | After 27.6 mo. |
|      | Shape is slightly indistinct | More slightly indistinct than last time |
|      | Distribution is grouped | Disappearance |
|      | More reduction | Disappearance |
| 2    | Pretreatment | After 1 mo. | After 8.9 mo. | After 15.2~30 mo. |
|      | Shape is branching & casting calcification | Unchanged |
|      | Distribution is grouped | Disappearance |
|      | More reduction | Disappearance |
| 3    | Pretreatment | After 1.6 mo. | After 3.5 mo. | After 9.8~21 mo. |
|      | Shape is slightly indistinct | Reduction |
|      | Distribution is grouped | More reduction |
|      | Disappearance | |
| 4    | Pretreatment | After 8.6 mo. | After 12.6 mo. |
|      | Shape is small round containing linear | Disappearance |
|      | Distribution is grouped | |
| 5    | Pretreatment | After 3.7 mo. | After 13 mo. |
|      | Shape is slightly indistinct | Disappearance |
|      | Distribution is grouped | Disappearance |
| 6    | Pretreatment | After 5.9 mo. | After 13.6 mo. | After 19.4 mo. |
|      | Shape is pleomorphic | Unchanged |
|      | Distribution is segmental | Reduction |
|      | Unchanged from last time | |
| 7    | Pretreatment | After 3.0 mo. | After 12 mo. |
|      | Shape is pleomorphic | Reduction |
|      | Distribution is grouped | More reduction |
| 8    | Pretreatment | After 4.3 mo. | After 15.3 mo. |
|      | No calcification | No calcification |
| 9    | Pretreatment | After 3 mo. | After 14 mo. | After 18.6~33.4 mo. |
|      | No calcification | No calcification |
| 10   | Pretreatment | After 3 mo. | After 14 mo. | After 18.6~33.4 mo. |
|      | No calcification | No calcification |
|      | No calcification | No calcification |
**Figure 1.** Case 2. Aged patient (79F) with left breast cancer (cT2N0M0) treated with radiosensitization (KORTUC II). A ~ F: Pre and post-KORTUC II treatment evaluation of changes of tumor shadows on MMG. a ~ f: Profile curve of changes of tumor shadows (1 pixel = 93.9 μm). G, H: PET-CT images before KORTUC II (G) and 13 months after KORTUC II (H). (G) Tumor diameter is 22 mm (SUV\text{MAX} = 7.4). (H) There is neither local recurrence nor distant metastasis.
Figure 2. Case 4. 59 years old female patient with left breast cancer (cT2N0M0) treated with radiosensitization (KORTUC II). A ~ G: Pre and post-KORTUC II treatment evaluation of changes of tumor shadows on MMG. a ~ g: Profile curve of changes of tumor shadows (1 pixel = 93.9 μm). H, I: PET-CT images before KORTUC II (H) and 28 months after KORTUC II (I). (H) Tumor diameter is 27 mm (SUV\textsubscript{MAX} = 8.1). (I) There is neither local recurrence nor distant metastasis.
Figure 3. Case 6. Aged patient (79F) with left breast cancer (cT2N0M0) treated with radiosensitization (KORTUC II). A ~ C: Pre and post-KORTUC II treatment evaluation of changes of tumor shadows on MMG. a ~ c: Profile curve of changes of tumor shadows (1 pixel = 93.9 μm). D, E: PET-CT images before KORTUC II (D) and 4.6 months after KORTUC II (E). (D) Tumor diameter is 30 mm (SUV_{MAX} = 8.4). (E) There is neither local recurrence nor distant metastasis.

3. Discussion

Recently, breast-conserving surgery has become the most common surgical procedure for breast cancer treatment. However, even this type of surgery often has an unacceptable cosmetic outcome. Therefore, various types of minimally invasive options have been used as alternatives to surgical therapy, such as radiofrequency ablation (RFA), focused ultrasound ablation (FUS), and cryotherapy. These minimally invasive approaches are currently being investigated. Although excellent locoregional control can be obtained with these procedures, long-term control rates remain unknown. Moreover, RFA and cryotherapy demand insertion of a relatively large needle into the breast. General anesthesia
is essential to perform RFA, and FUS is very time-consuming and requires MRI to monitor the thermal
distribution. It is also important to note that these non-surgical approaches require adjuvant radiation
therapy to non-ablated tissue in order to eliminate residual cancerous tissue.

KORTUC II, a form of radiation therapy intensified with a newly-developed radiosensitizer for
intratumoral injection, is a logical technique for the ablation of cancerous nests throughout the breast.
KORTUC II has an advantage over other non-surgical ablation therapies, as it can treat breast cancer
with one treatment. General anesthesia, insertion of a large needle, and expensive equipment to
monitor thermal distribution are unnecessary with this method.

Precise assessment of therapeutic efficacy is important when evaluating breast cancer treatments.
MMG has been reported to be reliable for the detection of breast tumors and microcalcifications.
Therefore, this study used MMG and PET-CT as diagnostic tools for the assessment of the therapeutic
effects of KORTUC II on primary breast tumors. Tumors disappeared on MMG in several months
following KORTUC II treatment. Moreover, PET-CT confirmed that the absence of recurrence and
distant metastasis. Therefore, KORTUC II is considered to be an ideal non-surgical treatment for
elderly patients with early stages breast cancer.

4. Patients and Methods

Ten elderly female patients with breast cancer (invasive ductal carcinoma) but no clinical evidence
of distant metastasis 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 1. Patients were eligible
for this study if they had contraindications to general anesthesia due to old age and/or significant
cormorbidity, or they had declined surgical treatment.

For each patient, radiation therapy (RT) with 4 MV X-ray was delivered with an EXL-20TP linear
accelerator equipped with a multileaf collimator (Mitsubishi Electric Co. Ltd., Tokyo, Japan) [10,11].
Hypofractionated RT was administered using a tangential field approach & a Field-in-field method: the
total dose was 44 Gy administered as 2.75 Gy/fraction. RT was performed five times per week for each
patient. Boost irradiation was 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 RT with 4 MV X-ray.

The new radiosensitizer was injected into the breast tumor tissue twice a week under
ultrasonographic guidance, just prior to each administration of RT from the 6th fraction onwards. At the
injection of the agent, small amount of 1% lidocaine hydrochloride was used for pain relief at the
injection site. The agent is composed of 0.5% hydrogen peroxide and 0.83% sodium hyaluronate,
which is safe for injection and effectively preserves oxygen concentration in the tumor tissue for more
than 24 hours following intratumoral injection [12]. For sodium hyaluronate, we used one syringe
(2.5 mL) of a hyaluronic acid preparation having a 1% w/v concentration of sodium hyaluronate (ARZ
Dispo, Seikagaku Corporation, Tokyo, Japan). To this, 0.5 mL of a 3% w/v solution of hydrogen
peroxide in a vial subdivided aseptically at the pharmacy department of our hospital (Oxydol, Ken-ei
Pharmaceutical Co. Ltd., Osaka, Japan) was added immediately before use, and mixed well to prepare
the radiosensitizer.
Hormonal status was examined on a specimen obtained by needle biopsy at pre-treatment. Patients with estrogen receptor-positive tumors also underwent hormonal therapy using aromatase inhibitor for five years following KORTUC II. MMG was performed approximately twice a year during follow-up according to the Japanese Standard Methods established by the Japanese Central Committee on Quality Control of Mammographic Screening.

The therapeutic effects of KORTUC II were evaluated in terms of the changes in size of tumor shadows and microcalcifications shown on the monitor (3M pixel, Nanao Co. Ltd., Japan) before and following KORTUC II. Changes of tumor density on MMG were also analyzed using image analysis software image-J (National Institutes of Health, Bethesda, Maryland, USA). PET-CT was also performed annually during follow-up to detect both distant metastasis and local recurrence.

5. Conclusions

We conclude that breast-conservation treatment using KORTUC II followed by aromatase inhibitor is a promising therapeutic method for elderly patients with breast cancer, in terms of avoiding any surgical procedure. Moreover, MMG is considered to be useful for evaluating the efficacy of KORTUC II.

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