Non-surgical breast-conserving treatment using Kochi oxydol-radiation therapy for unresectable carcinomas II for patients with stage 0 to IIIC breast cancer

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Abstract. Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas (KORTUC) is a novel radiosensitizing treatment developed in Japan that involves intratumoral injections of hydrogen peroxide (H_2O_2) and sodium hyaluronate (HA). KORTUC II, an evolved form of the therapy, aims to enhance radiotherapy efficacy by locally increasing oxygen tension and inhibiting antioxidant enzymes in the tumor microenvironment. This study retrospectively evaluated the safety and efficacy of KORTUC-based breast-conserving therapy (KORTUC-BCT) in patients with stage 0-IIIC primary breast cancer who refused standard treatment protocols. A total of 50 patients who underwent KORTUC-BCT between February 2013 and April 2022 and had at least 1 year of follow-up were included. Radiotherapy consisted of short-course tangential irradiation at a dose of 44 Gy in 16 fractions. For patients with lymph node metastases, the supraclavicular region was included in the radiation field. A boost dose of 9-12 Gy was subsequently delivered to the tumor using electron-beam radiation therapy. The H_2O_2/HA sensitizer was intratumorally injected twice weekly under ultrasound guidance. All patients achieved a clinical complete response within a median evaluation time of 12 months. The 3-year local control rate for all cases was 89.3%; by stage, it was 100% for 0-I, 100% for IIA, 53.3% for IIB, 75% for IIIA, 75.0% for IIIB and 100% for stage IIIC. The 3-year disease-free survival rate was 75% overall; by stage, it was 100% for 0-I, 91.7% for IIA, 53.3% for IIB, 60.0% for IIIA, 75.0% for IIIB and 20.0% for IIIC. Lymph node metastasis sites had a 100% 3-year control rate. No grade ≥3 adverse events or cosmetic complications were observed. These findings suggest that KORTUC-BCT is a minimally invasive and well-tolerated therapy with promising outcomes, particularly for patients with early-stage breast cancer who decline surgery. This clinical study was registered in the UMIN clinical trials registry (UMIN000003734; June 10, 2010).

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Introduction

KORTUC (Kochi Oxidol-Radiation Therapy for Unresectable Carcinomas) was proposed and developed by Kochi University in 2006 and is currently the most widely used radiosensitizer in clinical practice in Japan. Ogawa *et al* (1) developed a novel treatment method (KORTUC II), in which hydrogen peroxide is locally injected into tumors as a new type of radiosensitizer, and confirmed its safety and efficacy in patients with locally advanced cancers (2,3). Hydrogen peroxide (H_2O_2) is the only agent known to inactivate antioxidant enzymes and simultaneously generate oxygen when injected into tumor tissues (1-3).

KORTUC I involves the application of a sensitizer to the tumor surface, whereas KORTUC II is an advanced formulation that allows direct intratumoral injection. The solution consists of 0.5% H_2O_2 and 0.83% sodium hyaluronate (HA). H_2O_2 is the active component of the radiosensitizer, and HA functions to delay its decomposition, thereby maintaining an elevated oxygen concentration within the tumor for a sustained period. A characteristic feature of KORTUC II is the injection of these two components at a specific ratio.

Since May 2010, Osaka Medical and Pharmaceutical University has clinically implemented this treatment and has treated over 400 patients with combined KORTUC I and II. The effectiveness of KORTUC has previously been reported in cases of recurrent and locally advanced breast cancer.

Currently, a Phase II trial targeting locally advanced and recurrent breast cancer is underway in the United Kingdom (NCT03946202), and various clinical studies targeting different solid tumors are in progress in Japan.

Although standard treatment is generally recommended for primary breast cancer, some patients refuse surgery or drug therapy due to cosmetic concerns, comorbidities, or personal preferences, and alternative approaches are limited for these individuals. In this report, we present a case series of breast-conserving therapy using KORTUC (KORTUC-BCT) for patients with primary breast cancer stages 0-IIIC who declined standard treatment.

Materials and methods

Patient selection. KORTUC therapy was administered to patients with newly diagnosed primary breast cancer who had no distant metastases and had refused standard treatments such as surgery. All patients provided written informed consent after receiving a detailed explanation of the procedure. Hormonal therapy or systemic chemotherapy was administered in some cases, based on the clinical judgment of the attending breast surgeon and patient preference.

The present KORTUC II clinical study was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University [Trial no. 1973, May 10, 2010; UMIN Clinical Trials Registry, UMIN000003734, June 10, 2010].

Method for dosing the KORTUC sensitizer. The sensitizer consisted of 0.83% HA and 0.5% H_2O_2 (H_2O_2, also known as 'oxydol' in Japan). It was prepared aseptically before each use by adding 2.5 ml of HA (Adant Dispo) and 1 ml of 1% xylocaine to 0.5 ml of oxydol, mixing them into a total volume of 4 ml in a single vial. Our standard dosing protocol prescribed one vial for tumors <3 cm in diameter, two vials for tumors 3-<5 cm, and ≥3 vials for tumors ≥5 cm in diameter, with a maximum dose of five vials for giant tumors. However, the optimal dose remains unclear. The sensitizer was administered intratumorally under direct vision or with ultrasound or computed tomography (CT) guidance twice weekly immediately before each radiotherapy session. Under ultrasound guidance, when the sensitizer is injected into a tumor, oxygen is generated in the form of microbubbles, and the tumor is immediately recognized as a high-echo area.

The sensitizer is injected to distribute oxygen throughout the tumor. Usually, sensitizer injections are administered after the patient has received approximately 20 Gy at the beginning of the radiotherapy course. This was to prevent increased intratumor pressure from the injections, causing viable tumor cells to infiltrate the nearby lymphatic and blood vessels (4). To prevent dissemination along the injection route, punctures were made on the skin surface in the irradiation field whenever possible. When multiple lesions were present within the irradiation field, the sensitizer was injected into both the primary and accessible subcutaneous lesions under ultrasound guidance. The injection was administered through the skin within the irradiated field whenever possible, to avoid seeding along the needle tract. In cases of lymph node metastases, sensitizer injections were administered only when the nodes were sufficiently large to be safely punctured, considering the associated risks.

Table I. Patient characteristics.

Variable	Total
Patients, n (range)	50
Median age, years	57 (29-83)
Median follow-up period, months	27 (12-95)
Clinical stage, n (%)	
0	2 (4.0)
I	12 (24.0)
IIA	17 (34.0)
IIB	5 (10.0)
IIIA	5 (10.0)
IIIB	4 (8.0)
IIIC	5 (10.0)
Chemotherapy, n (%)	
Yes	7 (14.0)
No	43 (86.0)
Hormone therapy, n (%)	
Yes	29 (58.0)
No	21 (42.0)
Molecular subtype, n (%)	
Luminal A or B	38 (76.0)
Luminal HER2	6 (12.0)
HER2	3 (6.0)
Triple negative	1 (2.0)
Unknown	2 (4.0)

Radiotherapy. Radiotherapy was administered according to standard hypofractionation protocols. For stage 0-IIA, all patients received whole-breast irradiation with tangential fields at a dose of 44 Gy in 16 fractions, followed by a tumor bed boost of 9 Gy in three fractions. For patients with stage IIB-IIIC disease, the supraclavicular and internal mammary lymph node areas were included depending on the case. The total dose ranged from 53 to 56 Gy in 19-20 fractions (tangential field, 44 Gy/16 fractions; boost, 9 Gy/3 fractions in 18 patients, and 12 Gy/4 fractions in one case). X-rays were used for tangential irradiation, and either X-rays or electron beams were used for boost irradiation.

Items examined. The treatment efficacy was comprehensively evaluated using computed findings from CT, magnetic resonance imaging, positron emission tomography/CT, breast ultrasonography, and mammography. The local control duration was defined as the time from the end of radiotherapy to the point at which tumor regrowth was confirmed by imaging within the irradiated fields. Local control and overall survival (OS) rates were estimated using the Kaplan-Meier method.

Statistical analysis. The survival time was calculated from the day after treatment completion. Continuous variables are expressed as mean ± standard deviation, and categorical variables are presented as numbers (percentages). Survival analyses were conducted using the Kaplan-Meier method, and comparisons were made using the Wilcoxon rank-sum

Table II. recurrence pattern.

Clinical stage	Site of recurrence	Time to recurrence, months
I	Local	47
IIA	Liver	13
IIB	Local, ovary, bone, gluteal muscle	18
IIB	Local	28
IIIA	Local	20
IIIA	Local, liver, lung, bone	6
IIIB	Contralateral lymph node	12
IIIC	Bone	30
IIIC	Brain	22
IIIC	Bone	9
IIIC	Liver	11

test. Differences between groups, including comparisons by radiation dose, were analyzed using the Wilcoxon rank-sum test. Statistical analyses were performed using the EZR software (version 1.54) and Microsoft Excel 2016. Statistical significance was set at $P<0.05$.

Results

Between February 2013 and April 2022, 50 patients underwent KORTUC breast-conserving therapy (KORTUC-BCT) and were followed for at least 1 year. Patient characteristics are summarized in Table I. All patients were female, with a mean age of 57 years (range: 38-83 years). The staging distribution was as follows: stage 0 (n=2); stage I (n=12); stage IIA (n=17); stage IIB (n=5); stage IIIA (n=5); stage IIIB (n=4); and stage IIIC (n=5). The molecular subtypes were Luminal A (n=30), Luminal B (n=8), Luminal-HER2 (n=6), HER2 (n=3), triple negative (n=1), and unknown (n=2).

The median radiation dose was 53 Gy delivered in 19 fractions. The number of sensitizer injections ranged from four to six, with a median of five injections. Among the 50 patients, 29 received hormone therapy and seven received chemotherapy. Notably, 17 patients (34.0%) refused hormone therapy, and among 34 patients with tumors classified as T2 or higher, 28 (82.3%) refused chemotherapy. The median follow-up period was 27 months (range, 12-95 months). All patients initially achieved a clinical complete response (cCR) with a median time to cCR of 12 months (range: 5-33 months). Recurrence occurred in 11 patients: five experienced local recurrence, and eight experienced distant recurrence (two had both) (Table II). The 3-year OS rate for all patients was 98.0% (95% CI: 86.4-99.7), with no disease-specific deaths during the observation period. One patient died of an unrelated disease (bladder cancer) (Fig. 1).

The overall 3-year local control rate was 89.3% (95% CI: 72.5-96.0). When analyzed by clinical stage, the 3-year local control rates were 100% for 0-I and IIA, 53.3% for IIB, 75.0% for IIIA, 75.0% for IIIB, and 100% for IIIC (Fig. 2A and B). The 3-year disease-free survival (DFS) rate for all patients was 80.9% (95% CI: 62.6-90.8). Stage-specific analysis revealed 3-year DFS rates of 100% for 0-I, 91.7% for IIA, 53.3% for IIB, 60.0% for IIIA, 75.0% for IIIB, and 20.0% for IIIC (Fig. 3A and B). Among the node-positive patients, the 3-year local control rate for primary tumors was 72.9% (95% CI: 41.4-89.3), (Fig. 4A), and the 3-year control rate for metastatic lymph nodes was 100% (Fig. 4B). In patients with stage IIB-IIIC disease and lymph node metastases, comparison between those with and without chemotherapy showed 3-year DFS and local control rates of 38.8% (95% CI: 13.3-64.2) and 64.2% (95% CI: 28.8-85.7), respectively, in the non-chemotherapy group and 75.0% (95% CI: 12.8-96.1) and 100%, respectively, in the chemotherapy group. Although the differences were not statistically significant (P=0.347 and P=0.238), this trend favored chemotherapy (Fig. 5A and B). No Grade 3 or higher acute adverse events were observed. The only reported acute reaction was mild pain during the sensitizer injection. No significant cosmetic deterioration was observed following treatment.

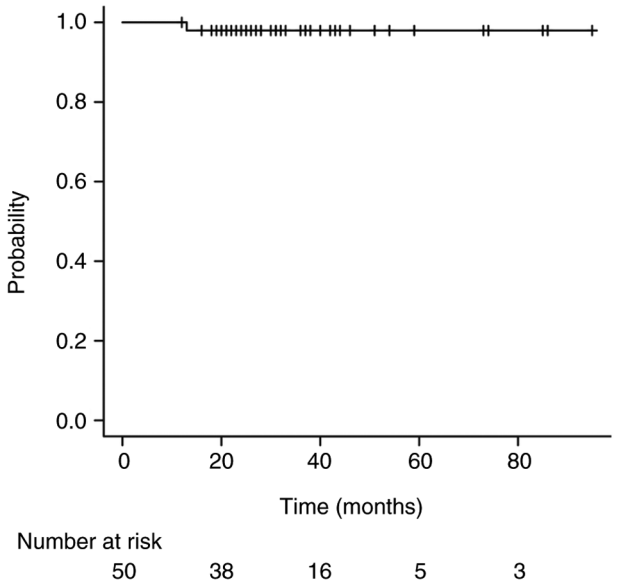

Figure 1. Overall survival. The median follow-up was 27 months, and the 3-year overall survival was 98%.

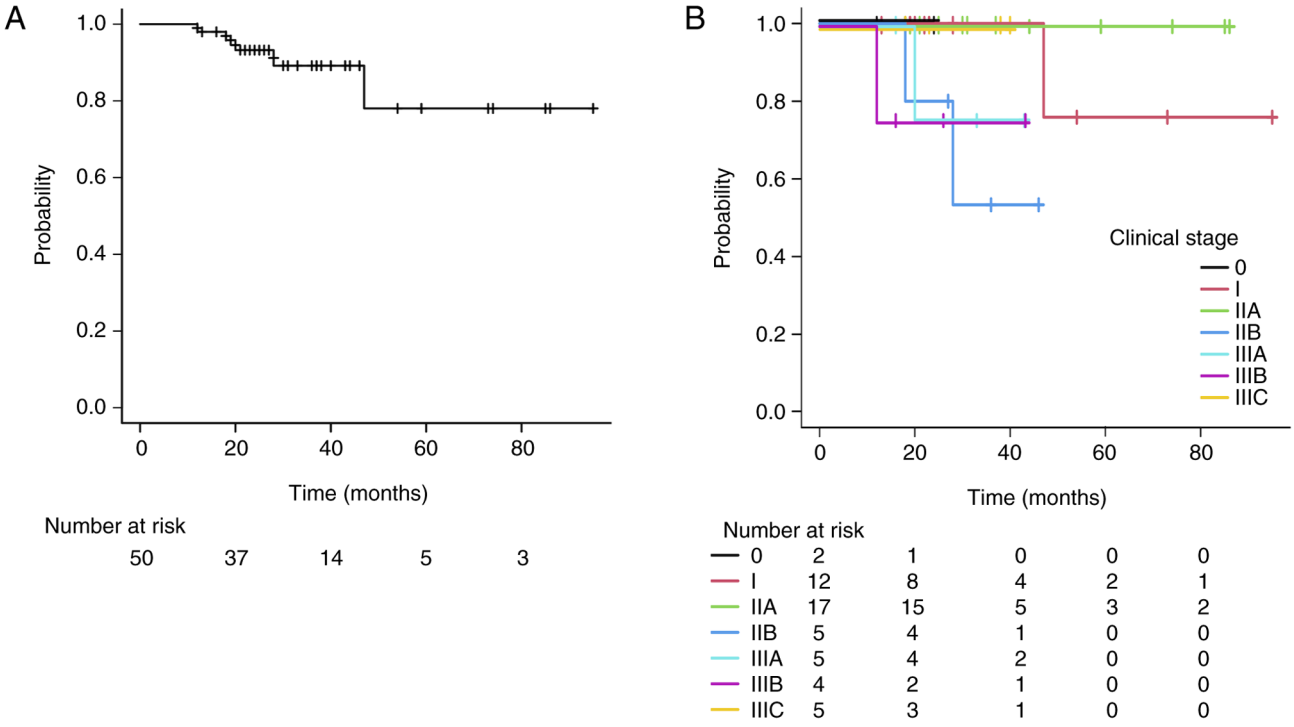

Figure 2. Local control late. (A) 3-year LCR was 89.3%. (B) LCR according to clinical stage. The 3-year LCRs were 100% for 0-I and IIA, 53.3% for IIB, 75% for IIIA,75% for IIIB, and 100% for IIIC. LCR, local control rate.

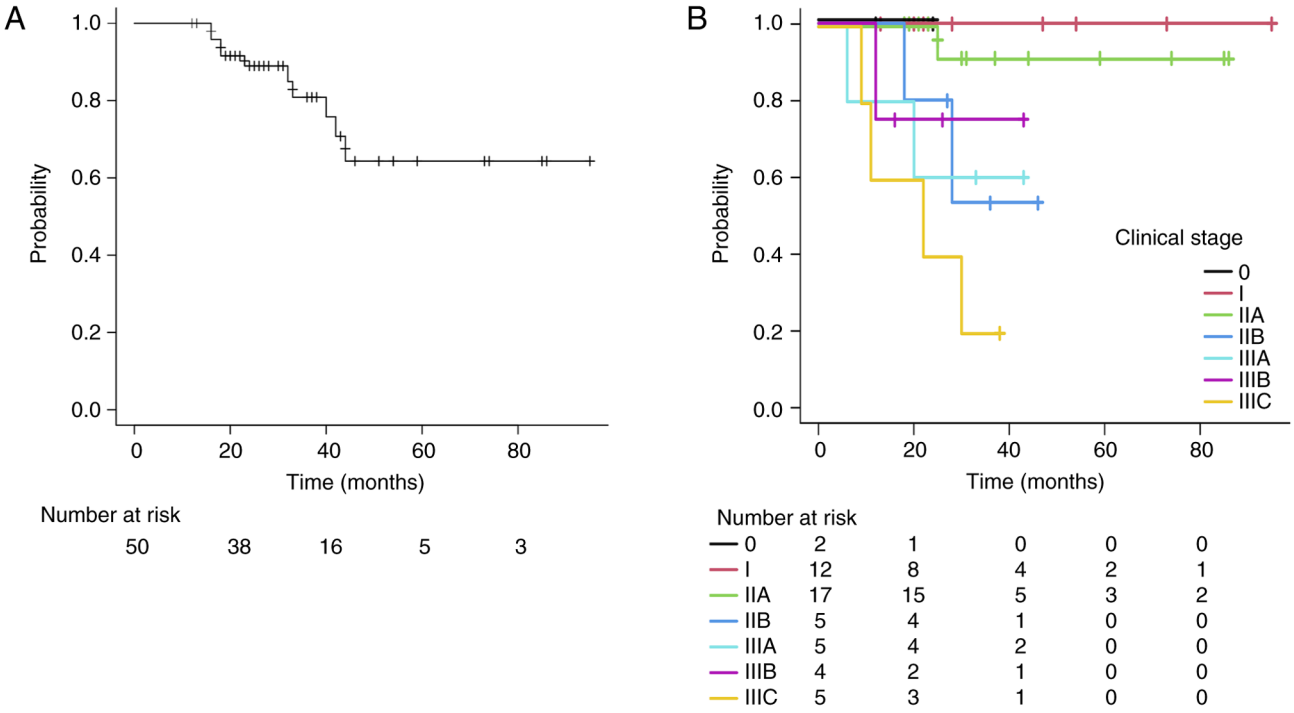

Figure 3. DFS rate. (A) 3-year DFS rate was 80.9%. (B) DFS rate according to clinical stage. The 3-year DFS rates ware 100% for 0-I, 91.7% for IIA, 53.3% for IIB, 60.0% for IIIA, 75.0% for IIIB and 20.0% for IIIC. DFS, disease free survival.

Discussion

KORTUC II is a novel enzyme-targeting radiosensitization therapy developed at Kochi University and is the world's first radiosensitizer designed for intratumoral injection (1-3). This treatment is compatible with conventional linear accelerators (linacs) used in most radiotherapy facilities. The combination of H_2O_2 and HA in KORTUC inactivates the antioxidant enzyme peroxidase within tumor tissues. This inactivation results in oxygen generation, increased oxygen tension, and enhanced X-ray-induced free-radical effects. Due to the limited peroxidase activity in cancer cells, intracellular accumulation

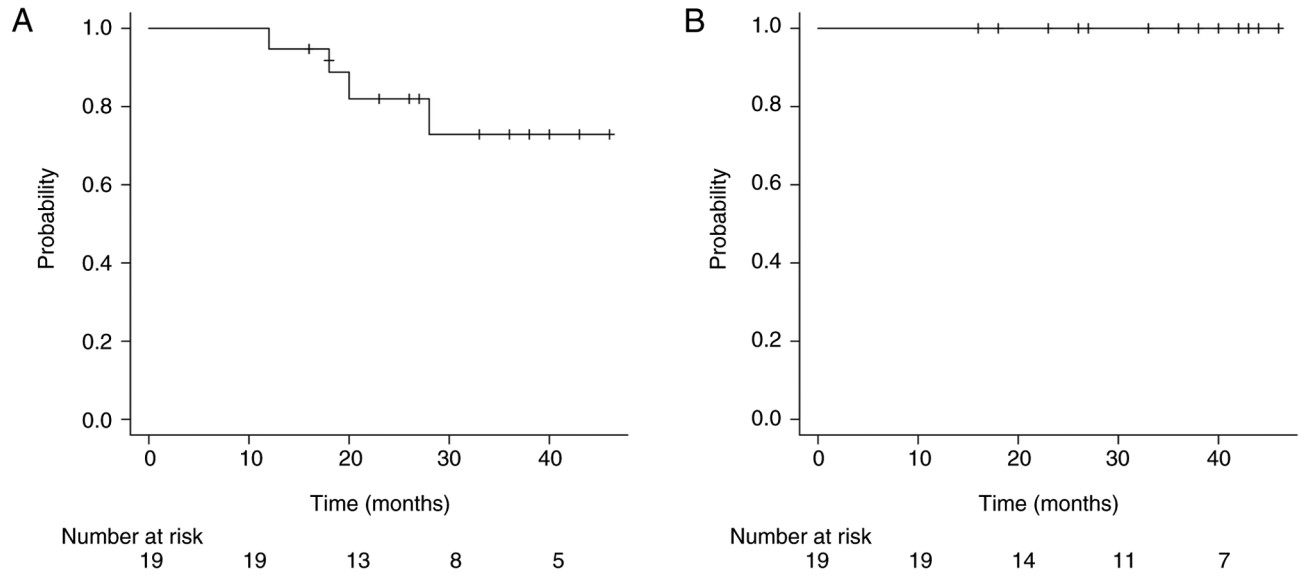

Figure 4. Local control rates in patients with metastatic lymph nodes. (A) Primary tumor control rate in patients with metastatic lymph node. The 3-year local control rate for the primary tumors was 72.9%. (B) Metastatic lymph node control rate. The 3-year control rate of metastatic lymph nodes was 100%.

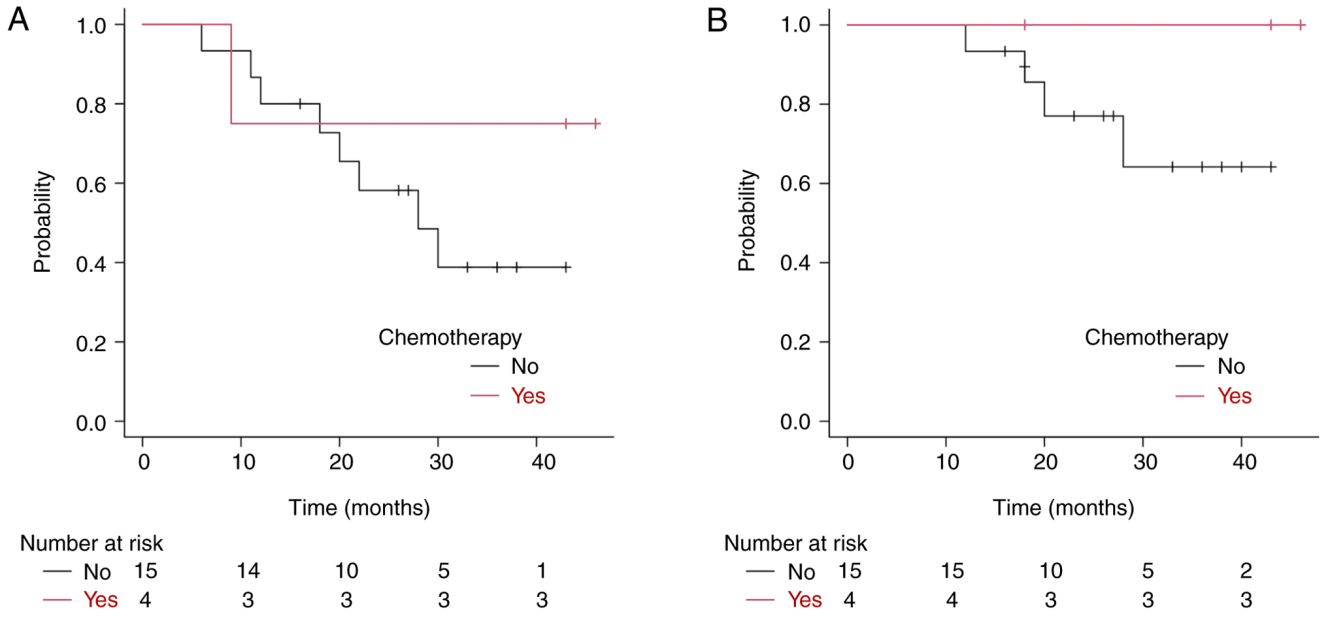

Figure 5. Comparison of treatment outcomes with and without chemotherapy in patients with stage IIB-IIIC. (A) Comparison of DFS rates with and without chemotherapy in patients with stage IIB-IIIC. The 3-year DFS rate was 38.8% in patients in the non-chemotherapy group, whereas it was 75% in the chemotherapy group. There was no significant difference between the two groups (P=0.347). (B) Comparison of LCR with and without chemotherapy in patients with stage IIB-IIIC. The 3-year LCR was 64.2% in the non-chemotherapy group, whereas it was 100% in the chemotherapy group. There was no significant difference between the two groups (P=0.238). DFS, disease free survival. LCR, local control rate.

of H_2O_2 occurs, promoting apoptosis via the mitochondrial and lysosomal pathways (5,6).

Through this mechanism, KORTUC transforms radiation-resistant cells into radiation-sensitive cells, significantly enhancing the efficacy of low-LET radiation, such as X-rays (4,7,8). When H_2O_2 is injected alone, it causes severe local pain and rapid diffusion of oxygen, thereby preventing sustained oxygen tension. However, the addition of HA not only reduces pain but also sustains intratumoral oxygenation for up to 24 h (5,9). As both components are naturally occurring substances in the human body-H_2O_2 in saliva and hyaluronate in connective tissues-KORTUC is considered a highly safe radiosensitization method.

This study demonstrated favorable local control and OS with KORTUC-BCT. For early-stage (0-IIA) breast cancer, the 3-year local control and DFS rates were 100 and 94%, respectively. Ogawa *et al* previously reported a 5-year progression-free survival rate of 97.1% in patients with stage I-II disease (1). Historically, radiation monotherapy has been used for inoperable or older patients with breast cancer, often with conventional fractionation, yielding modest results; 3-year local control rates range from 45 to 57% (10-12).

Techniques such as radiofrequency ablation (RFA) have reported complete pathological responses of 30-100% (mostly over 60%) after resection (13-18), and high-intensity focused ultrasound (HIFU) has shown complete necrosis rates between 17 and 100% (14,19-22). However, these methods often require subsequent surgery for confirmation and are limited in scope.

For stage IIB-IIIC cases, the 3-year local control rate was 72.9%, although the DFS rate was lower at 48.2%, with distant metastasis occurring in more than half of the advanced cases. Among patients with T2b or higher tumors, approximately 80% refused chemotherapy and 40% refused hormone therapy (HT). Given the systemic nature of breast cancer, local treatments alone, such as KORTUC, are insufficient for advanced cases. Chemotherapy notably improved the 3-year DFS rate, from 38.8% (without chemotherapy) to 75% (with chemotherapy). Although this difference was not statistically significant due to the small sample size, the trend suggests that combining chemotherapy with local treatment is preferable. Although we did not perform an analysis by molecular subtype in this study, we carefully explained to patients with high-grade tumors or high recurrence risk that, despite good local control, distant metastases may still occur and strongly recommended systemic therapy in conjunction with KORTUC treatment.

Remarkably, the 3-year control rate for metastatic lymph nodes within the irradiation field was 100%. HA has high lymphatic affinity, and studies in rats have shown rapid migration (within 5 min) to adjacent lymph nodes (23,24). This supports the hypothesis that KORTUC injected into the tumor may migrate to the lymph nodes and enhance radiosensitization. Distant metastasis occurred in 8 patients, involving 12 sites, primarily in stage IIA or higher. The sites included the bone (n=4), liver (n=3), lungs (n=1), brain (n=1), ovary (n=1), muscle (n=1), and contralateral lymph nodes (n=1), predominantly via hematogenous spread. The potential for the abscopal effect, a systemic antitumor response induced by localized radiation, is of particular interest. KORTUC has demonstrated such effects through immune activation in murine models, especially when combined with PD-1 blockade (25). However, its abscopal efficacy in the clinical setting has not yet been proven.

This study highlights the potential of KORTUC as an alternative for patients who refuse standard therapies, respecting individual values, and enabling personalized treatment. For patients seeking cosmetic preservation or avoiding surgery, the KORTUC-BCT offers a promising nonsurgical option. Other non-surgical modalities, such as RFA and HIFU (21,26-28), have limitations; RFA requires large-bore needle insertion under local anesthesia, and HIFU is suitable only for small (<10 mm), superficial tumors with adequate fat tissue, making KORTUC potentially more beneficial.

This study has several limitations. A sample size was relatively small, which may limit the generalizability of the findings. The retrospective design of the study inherently carries the risk of selection bias and limits the ability to establish causal relationships. Although early outcomes appear promising, the follow-up period was relatively short for a breast cancer study, making it difficult to assess long-term efficacy and safety. To validate the clinical utility of KORTUC II, further prospective studies with larger patient cohorts and longer follow-up periods are warranted.

Effective administration of KORTUC requires skill, and the tumor location and morphology affect the technique. However, the optimal dose remains undefined, necessitating further quantitative studies. Currently, dosing is based on tumor size; however, the future integration of imaging analysis and AI-based prediction models is anticipated. KORTUC demonstrated remarkable local control beyond that achieved with radiation therapy alone. Its efficacy has been reported for other solid tumors, including cervical, pancreatic, and rectal cancers (17,29-31). With proper techniques and attention paid to the risks of intravascular injection, it remains a safe radiosensitizer. A phase II trial for advanced breast cancer is ongoing in the UK, and phase I trials for cervical and rectal cancers are scheduled to begin this year. KORTUC may also be a viable treatment option for patients with primary breast cancer who have declined standard therapies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AH, TS and KeN designed the study and wrote the manuscript. AH, TS and MN analyzed and interpreted the patient's clinical data. AH, TS, JI, TI, MM, KKo, TO, AK, YY, ST and HY performed the KORTUC treatment and statistical analysis. KaN, HA, KY, KKi and MI contributed to collecting the relevant literature and performing the data analysis. AH and TS confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present KORTUC II clinical study was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University (trial no. 1973, May 10, 2010; UMIN Clinical Trials Registry, UMIN000003734, June 10, 2010). All the patients provided written informed consent after receiving a detailed explanation of the procedure.

Patient consent for publication

The patients provided written informed consent for publication.

Competing interests

The authors declare that they have no competing interests.

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