New Enzyme-Targeting Radiosensitizer (KORTUC II) Treatment for Locally Advanced or Recurrent Breast Cancer

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Abstract

Purpose

Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas II (KORTUC II) is currently the most widely used radiosensitizer in clinical use in Japan. Its use sensitizes tumors to radiation by injecting hydrogen peroxide into the tumors to neutralize antioxidant enzymes and, simultaneously, increase intratumor oxygen tension. KORTUC II has achieved significant local effects with no notable adverse events. We report on the cases where KORTUC II was used to treat patients with locally advanced breast cancer (LABC) or recurrent breast cancer (LRBC).

Methods and Materials

Thirty patients treated with KORTUC II for LABC (n = 9) or LRBC (n = 21), who were followed up for at least 3 months after treatment, were included in the study. This sensitizer is a solution consisting of 0.83% sodium hyaluronate and 0.5% hydrogen peroxide by volume. The mixture was injected intratumorally several times during the treatment period under ultrasound guidance, just before RT doses. RT was administered for local control. The irradiation dose and extent fields were determined by the attending physicians considering patient factors. Maximum tumor shrinkage (MTS) was measured by Computed Tomography. The duration of loco-regional control (LC) and progression free survival (PFS) after the completion of RT were determined using the Kaplan–Meier method.

Results

The median irradiation dose was 60.4 Gy3.5 (43.6–76.1 Gy3.5) based on the calculation of EQD2, and median total number of sensitizer treatments was 5 (2–7). The median MTS was 97.0%. Fifteen patients (50%) were assessed to have achieved a clinical complete response. The proportion of patients with LC at 1, 2, and 3 years was 100%, 94.7%, and 75.4%. The proportion with PFS after RT at 1 and 2 years was 59.0%, and 24.1%, respectively.

Conclusions

KORTUC II treatment demonstrated high rates of local tumor control for LABC and LRBC. KORTUC II is expected to be an inexpensive and extremely promising RT with an excellent radio-sensitizing effect.

Trial registration

Osaka Medical College Clinical Trials Registry, trial no. 1973, date. May 10, 2010

UMIN Clinical Trials Registry, trial no. UMIN000003734, date. June 10, 2010

1. Introduction

Symptoms such as bleeding and tissue breakdown due to progression of locally advanced breast cancer (LABC) and locally recurrent breast cancer (LRBC) are events that lead to a reduction in quality of life (QOL), and it is often difficult to deal with them because the symptoms cannot be alleviated at the terminal stage. Surgical treatment is difficult for advanced lesions that cannot be controlled by radiation therapy (RT). If RT enables local control, the patient's QOL will improve. However, LABC and LRBC are often situations in which drug therapy is ineffective, and it is difficult to obtain local control with RT alone, because such lesions contain numerous hypoxic cancer cells and antioxidant enzymes that may confer resistance to RT. [1–3]

As reported in past studies [1–5], a novel radiosensitizer, Kochi Oxydol Radiation Therapy for Unresectable Carcinomas II (KORTUC II), was developed for the treatment of cancers that contain numerous hypoxic cancer cells and antioxidant enzymes. Following KORTUC II therapy, hypoxic and radioresistant cancer cells become hyperoxic and radiosensitive. The

concept of KORTUC II is to transform radioresistant cancer into radiosensitive cancer. [1–6] KORTUC II was first used in Kochi University in 2006 and is currently the most widely used radiosensitizer in clinical practice in Japan. Our institution has used KORTUC (I + II) in over 250 patients to date since the first patient was treated in May 2010 after obtaining approval from the University's Ethics Committee. (KORTUC I involves application of the sensitizer to neoplastic surface tissue rather than injecting the sensitizer into tumor tissue.) KORTUC II has achieved significant local effects with no notable adverse events. In this article, we report on the cases where KORTUC II was used to treat patients with LABC or LRBC.

2. Subjects And Method

At our institution, KORTUC II treatment was performed after detailed informed consent was obtained from patients who were expected to survive at least a year and met the following additional criteria: (1) local control by conventional radiotherapy alone was presumed to be difficult; (2) the dosage of additional irradiation they could receive was limited; and (3) they refused surgery as a treatment option. Hormone therapy or systemic chemotherapy was used concomitantly in some patients according to the judgment of the attending breast surgeon and the patient's wishes. KORTUC II treatment was approved by the Ethics Committee of Osaka Medial College (May 10, 2010).

Of the 37 patients treated with KORTUC II for LABC or LRBC between February 2011 and January 2020, the 30 patients who were followed up for at least 3 months after treatment were included in the study. These subjects consisted of 9 patients with LABC (1 in stage IIIA, 5 in stage IIIB, and 3 in stage IV) and 21 patients with LRBC. (Fig. 1)

- Radiotherapy

RT was performed for the purpose of local control with external beam irradiation (X-ray or electron beam) to locally advanced lesions, recurrent lesions or metastatic lesions of the breast, chest wall, axillary lymph nodes, and supraclavicular fossa lymph nodes. The dose and extent, as well as particular tumor sites to be irradiated, were determined by the attending physicians considering factors including tumor size and location, concomitant therapies, presence/absence of metastases outside the irradiation fields, and general condition of the patient.

In principle, the irradiation fields were to include all lesions for stage III LABC, and local areas that required local control for stage IV LABC and LRBC patients.

- Dosing method of the sensitizer

This sensitizer is a solution consisting of 0.83% sodium hyaluronate and 0.5% hydrogen peroxide (H2O2, also known as "oxydol" in Japan) by volume. It is prepared aseptically before each use by adding 2.5 mL of sodium hyaluronate (Adant® Dispo) and 1 mL of 1% xylocaine to 0.5 mL of oxydol and mixing them to be dispensed as a total volume of 4 mL from a single vial. Our standard dosing protocol called for 1 vial for tumors < 3 cm in diameter, 2 vials for tumors 3–<5 cm in diameter, ≥ 3 vials for tumors ≥ 5 cm in diameter, with a maximum dose of 5 vials for giant tumors. However, the optimal dose is still uncertain.

The sensitizer was injected into the tumor twice weekly immediately before RT either under direct vision in the case of tumors close to the skin, or under ultrasound or CT guidance. Under ultrasound guidance, when the sensitizer is injected into a tumor, oxygen is generated in the form of micro-bubbles and the tumor can immediately be recognized as a high echo area. The sensitizer was injected so that oxygen was distributed in the entire tumor. Usually, injections of the sensitizer occurred after the patient had already received approximately 20 Gy at the beginning of a course of RT. This was to prevent the increased intra-tumor pressure from the injections causing viable tumor cells to infiltrate into nearby lymphatic and blood vessels.[5] To prevent dissemination along the injection route, punctures were made on the skin surface in the irradiation field, whenever possible.

- Items examined

To examine the local effects, the tumor size was measured before treatment and at the estimated time of greatest regression (smallest volume) within 2 years after treatment. From this, the maximum tumor shrinkage (MTS) was calculated according to the percent decrease in tumor volume revealed by CT imaging at the estimated time of greatest regression. The tumor volume was measured based on CT images using the Eclipse radiation treatment planning system (Varian Medical Systems, Inc.). This interval to greatest regression was determined based upon prior studies using contrast-enhanced MRI that show, on average, 14 months are required between KORTUC II therapy and tumor disappearance according to RESIST criteria. However, there is no pre-determined protocol for scheduling follow-up imaging tests., In particular, CT scans to evaluate treatment effects were performed in a timely manner depending on the situations of individual cases. In addition to the CT-determined volume measurements, MRI, and PET-CT imaging were conducted when deemed appropriate to assess the presence and extent of any residual tumor in the treated area. The duration of loco-regional control (LC) was determined by the time in months at which tumor regowth in the irradiated target lesion was noted by one of these imaging techiques, and this event indicated local recurrence. LC and duration of progression free survival (PFS) after the completion of RT were determined using the Kaplan–Meier method, and are shown in Figs. 4 – 1 and 4 – 2. In the case of LC and PFS, death of the subject was regarded a censoring event.

The irradiation dose was calculated as equivalents of 2 Gy fractions (EQD2) with an α/β ratio of 3.5 (breast cancer has a low ratio of α/β), and described as Gy3.5.[7,8] Additionally, the subjects were divided into two groups, less than 60 Gy3.5 (60Gy<) and 60 Gy3.5 or more (≧ 60Gy), and evaluated according to whether there was a statistically significant difference in number of sensitizer injections, MTS, duration of LC, and time to progression (TTP) using Student's t-test. Comparison of duration of LC and PFS between the two groups (60Gy<, ≧60Gy) was evaluated using the Kaplan–Meier method.

3. Results

Table 1 shows the baseline patient characteristics. All of the 30 patients were women, and the mean age was 61 years (43–75 years). RT was performed at the median dose of 53 Gy/19 Fr (40 Gy/16 Fr–67.5 Gy/25 F). The median irradiation dose was 60.4 $Gy_{3.5}$ (43.6–76.1 $Gy_{3.5}$). The median total number of sensitizer injections was 5 (2–7). Of the 30 patients, 22 patients were treated concomitantly with hormone therapy and 18 patients with chemotherapy. Concomitant treatment status for one patient was unknown. The median follow-up period was 19 months (3–106 months).

Table 1
Patient characteristics

Patient No.	Age	Disease	Stage	Irradiation site	Radiation dose (Gy)	Number of fraction	EQD2 Gy3.5	Number of sensitizer injections	Hormonal therapy	Chemo therapy
1	45	LRBC		CW	44	18	48	4	-	-
2	75	LRBC		CW	40	16	44	7	-	+
3	70	LABC	IIIB	CW, Ax	67.5	25	77	6	+	+
4	57	LABC	IV	CW, Ax	59	21	69	7	+	+
5	67	LRBC		CW	53	19	61	5	+	+
6	54	LRBC		Br, Ax	59	21	69	3	+	+
7	56	LRBC		CW	53	21	59	6	UK	UK
8	60	LRBC		Br	59.5	22	68	6	-	-
9	67	LRBC		CW, Ax	58	25	62	6	+	+
10	49	LRBC		Br	58.5	29	59	5	+	+
11	68	LRBC		Br, Ax	54	18	65	5	+	-
12	75	LRBC		Br	59	21	69	5	+	-
13	58	LRBC		CW	59	21	69	5	+	+
14	73	LRBC		CW	59	21	69	5	+	-
15	75	LRBC		Br	59	21	69	4	+	+
16	67	LRBC		CW, Ax, SC	60	30	60	3	+	-
17	59	LRBC		Ax, SC	60	30	60	5	+	+
18	72	LABC	IV	CW	44	16	51	3	+	+
19	51	LRBC		SC, Neck	60	30	60	2	-	+
20	74	LRBC		Br, Ax	53	19	61	5	+	+
21	74	LABC	IIIB	Br, Ax, SC	53	19	61	5	+	-
22	52	LRBC		CW	40	16	44	3	+	+
23	43	LRBC		CW	53	19	61	5	-	+
24	58	LRBC		Br	53	19	61	5	+	+
25	61	LRBC		CW	44	16	51	3	+	+
26	43	LABC	IIIA	Br, Ax, SC	53	19	61	5	-	+

Local advanced breast cancer (LABC), Local recurrence breast cancer (LRBC)

Breast(Br), Chest wall(CW), axilla(Ax), Supraclavicular fossa(SC), Unknown(UK)

Equivalent dose in 2 Gy fractions with the α/β ratio of 3.5 (EQD2 Gy3.5)

Patient No.	Age	Disease	Stage	Irradiation site	Radiation dose (Gy)	Number of fraction	EQD2 Gy3.5	Number of sensitizer injections	Hormonal therapy	Chemo therapy
27	48	LABC	IV	Br, Ax, s SC	53	19	61	5	+	-
28	59	LABC	IIIB	Br, Ax	53	19	61	5	+	-
29	52	LABC	IIIB	Br,Ax, SC	53	19	61	5	-	-
30	70	LABC	IIIB	Br, Ax, SC	53	19	61	5	+	-
Local advanced breast cancer (LABC), Local recurrence breast cancer (LRBC)										
Breast(Br), Chest wall(CW), axilla(Ax), Supraclavicular fossa(SC), Unknown(UK)										
Equivalent dose in 2 Gy fractions with the α/β ratio of 3.5 (EQD2 Gy3.5)										

Table 2 shows the therapeutic effects. The median baseline breast cancer tumor volume measured using CT, was 53.2 cm^3 and the mean volume was 116.5 cm^3 (4.2–642.5 cm^3). Following KORTUC II therapy, the median MTS was 97.0% (standard deviation = 9.8%) and the mean was 91.7% (range 77.2–100%) (Fig. 1). Fifteen patients (50%) were assessed to have achieved a clinical complete response (cCR) as a temporary effect. The median evaluation period until MTS was 8 months (2–17 months).

Table 2
Treatment effects

Patient No.	Pre-TTV (cm^3)	MTS (%)	Temporary effect	Time to MTS (M)	Regrowth in field	LC(M)	Regrowth out of field	TTP (M)	Follow up (M)	Prognosis
1	27.3	82.1	cPR	15	-	36	+	15	36	AWD
2	32.4	100.0	cCR	6	-	88	+	21	88	AWD
3	220.3	100.0	cCR	8	+	30	+	20	35	DOD
4	397.8	94.1	cPR	12	-	35	+	21	45	AWD
5	4.2	100.0	cCR	3	+	36	+	20	106	AWD
6	240.5	100.0	cCR	3	-	6	+	3	6	DOD
7	25.9	100.0	cCR	3	-	3	-	3	3	NED
8	446	77.0	cPR	2	-	3	-	3	3	AWD
9	179.6	86.4	cPR	12	+	37	+	37	46	DOD
10	26.9	88.1	cPR	13	-	28	+	6	28	DOD
11	642.5	100.0	cCR	8	-	21	+	4	21	AWD
12	71.9	100.0	cCR	17	-	28	-	28	28	DOAD (Pancreatic cancer)
13	176.9	78.7	cCR	10	-	72	+	4	72	AWD
14	25.3	100.0	cCR	5	-	33	-	33	33	NED
15	39	100.0	cCR	8	-	13	+	13	13	DOD
16	4.2	100.0	cCR	17	-	62	-	62	62	NED
17	29.5	100.0	cCR	9	-	59	+	11	59	AWD
18	260.1	84.5	cPR	12	-	37	+	4	37	AWD
19	68.2	90.8	cPR	5	-	8	+	1	8	DOD
20	65.6	76.1	cPR	12	-	25	+	5	25	AWD
21	23.7	100.0	cCR	16	-	16	-	16	16	NED
22	116.7	74.7	cPR	7	-	17	+	9	17	AWD
23	5.4	72.2	cPR	3	+	12	+	2	14	DOD
24	20.3	100.0	cCR	9	-	9	-	9	9	DOD
25	113.5	73.1	cPR	1	-	3	+	1	3	AWD
26	35.7	100.0	cCR	7	-	7	-	7	7	NED
27	7.2	100.0	cCR	5	-	11	-	11	11	NED
28	26.2	89.3	cPR	6	-	9	-	9	9	AWD

Pre-treatment tumor volume (Pre-TTV), Maximum tumor shrinkage (MTS), Local control (LC), Time to progression (TTP), Clinical complete response (cCR), Clinical partial response (cPR), No evidence of disease (NED), Alive with disease (AWD), Death of disease (DOD), Death of another disease (DOAD)

Patient No.	Pre-TTV (cm^3)	MTS (%)	Temporary effect	Time to MTS (M)	Regrowth in field	LC(M)	Regrowth out of field	TTP (M)	Follow up (M)	Prognosis
29	83.2	92.5	cPR	4	-	7	-	7	7	AWD
30	78.1	91.4	cPR	5	-	7	-	7	7	AWD

Pre-treatment tumor volume (Pre-TTV), Maximum tumor shrinkage (MTS), Local control (LC), Time to progression (TTP), Clinical complete response (cCR), Clinical partial response (cPR), No evidence of disease (NED), Alive with disease (AWD), Death of disease (DOD), Death of another disease (DOAD)

Tumor regrowth in treated lesions occurred in 4 patients (13.3%) at 30, 37, 36, and 12 months after treatment. The proportion of patients with enduring LC at 1, 2, and 3 years was 100%, 94.7%, and 75.4%, respectively, as shown in the Kaplan–Meier curve (Fig. 2 – 1) .

Seventeen patients (56.7%) presented with tumor exacerbation outside the irradiation field. The median duration of PFS was 9 months (2–62 months). Nine patients (30%) died –eight of the primary disease, and one of other disease (pancreatic cancer). The proportion of patients with PFS after RT at 1 and 2 years was 59.0%, and 24.1%, respectively, as shown in the Kaplan–Meier curve (Fig. <link rid="fig7">2</link>–2). Two patients (No. 6 and No. 23) developed chest wall necrosis in the irradiated area 2 and 3 months after RT, respectively.

Table 3 shows that the difference in the calculated EQD2 between the two groups, 60Gy < and ≧ 60Gy, was statistically significant ($p < 0.01$). On the other hand, there was no significant difference in number of sensitizer injections ($p = 0.40$), MTS ($p = 0.09$), duration of LC ($p = 0.49$), and TTP ($p = 0.30$). There was no difference in duration of LC ($p = 0.19$) and PFS ($p = 0.21$) between the two groups, as shown in the Kaplan–Meier curve (Fig. 3 – 1, 3 – 2).

Table 3
Differences in selected parameters according to whether subjects received < 60 Gy or > = 60 Gy (Student's t statistic).

		60Gy<	≧ 60Gy	p value
N		7 (23%)	23(77%)	
EQD2(3.5) (Gy)	avg.	50.2	63.5	< 0.01
Total number of injections	avg.	4.4	4.9	0.40
MTS(%)	avg.	86.1	93.4	0.09
Duration of LC (M)	avg.	30.3	23.7	0.49
TTP (M)	avg.	8.4	14.5	0.30

There was no significant difference in total number of sensitizer injections, MTS, duration of LC, and TTP.

4. Discussion

Radiosensitizers have been widely studied as a method to enhance the effects of RT. Although a number of radiosensitizers, including misonidazole, were developed in the past,[9–12] many of them have not been used in clinical settings due to adverse reactions such as peripheral neuropathy. In this context, KORTUC II, a new enzyme-targeting and radiation sensitizer developed at Kochi University, has gathered attention.[1–6] The sensitizer contains H2O2 and hyaluronic acid as its main components, which, along with their decomposition products, are harmless to the human body. This suggests it is a safe sensitizer if proper dosage is used and attention is paid to avoid procedural problems such as incorrect

administration into blood vessels.[5] The severity of acute-phase adverse events, such as radio-dermatitis, has been reported to be comparable with that following adjuvant radiation for regular breast-conserving therapy[13–15]. Also, no particular delay in acute-phase injuries has been observed. At our institution, we have used KORTUC II to treat over 250 cases of various solid cancers, including the LABC and LRBC reported in this article, but have observed no marked adverse reactions.

In our study, the 30 patients who underwent KORTUC II treatment experienced median MTS of 97%, the cCR rate was 50%, and the LC rate was 100%, 94.7%, and 75.4% at 1, 2, and 3 years, respectively (median follow-up period 19 months). Generally, excellent LC was obtained after therapy. Patients with LABC and LRBC have the potential for long term survival, and treatment that provides continuous symptom relief and local control is desired. The standard treatment for LABC is multidisciplinary treatment, with chemotherapy followed by local therapy (surgery and RT).[16–18] Twenty one of the 30 patients who received KORTUC treatment (70%) experienced tumor re-growth, despite all having received chemo or hormonal therapy. Even in these cases, tumor shrinkage was also observed and QOL was improved.

Regarding the radiation dose, it has been reported that irradiation of 30 Gy or more had a significant effect on symptom relief, and that patients who received 60 Gy or more at the primary site had a higher local control rate for 5 years compared with patients who received less than 60 Gy.[19.20] Sheldon et al concluded that high-dose RT without mastectomy is an effective means of local control of LABC.[19] In our case, we administered a high dose with a median 60.4 Gy3.5, but at this relatively high dose level there was no statistically significant difference in MTS, duration of LC and TTP depending on the irradiation dose. Although the responses of these 30 patients seems favorable considering their pre-treatment conditions, because individualized multidisciplinary treatment is used for LABC and LRBC, it would be difficult to compare the responses with those of patients who did not receive KORTUC II. Future well controlled cohort or retrospective case-control studies are necessary to address this issue.

Takaoka et al reported the in vivo efficacy of radiotherapy combined with prior intratumoral H2O2 injection. A dose-modifying factor of 1.3–1.5 would be expected when combined with fractionated radiotherapy.[21] If 3% H2O2 were injected alone, it would cause severe pain at the injection site. However, diluting the sensitizer fivefold with sodium hyaluronate reduces this pain to a mild level in the experience of our institution. In addition, mixing the moderately viscous sodium hyaluronate with the sensitizer retards its enzymatic breakdown and dispersion, resulting in an elevated oxygen partial pressure inside the tumor for over 24 hours.[3.4.6.22] Therefore, twice-weekly intra-tumor local injection may be the best regimen, considering the sensitizing effects, need to limit patient discomfort, and the effort of injection. Another major advantage is that H2O2 and sodium hyaluronate are inexpensive agents.

In addition, sodium hyaluronate itself may have the potential to suppress cancer progression and metastasis.[23–26] It has highly metabolized in the lymphatic system, and migrates readily via lymphatic capillaries to regional lymph nodes following injection into breast tumor tissue.[27–29] When accompanied by H2O2, these two compounds together can sensitize metastatic foci in lymph nodes. In the cases of KORTUC II treatment for first-episode breast cancer in our institution, we have experienced many cases of regression of axillary and supraclavicular fossa lymph node metastases in patients who received local injections of the sensitizer into the primary tumor, although none was injected into the metastatic nodes. CD44, which is highly expressed on the surface of cancer stem cells, is an adhesion molecule for which hyaluronic acid is a ligand.[26.30.31] This sensitizer is believed to target even the breast cancer stem cells.[14]

Generally, KORTUC II aimd for local tumor control and symptom relief in patients with LABC and LRBC. Patients with unresectable LABC and LRBC often have severely compromised QOL, due to massive exudation and bleeding from the lesion, odor, and disfigurement. NCCN guidelines version 5. 2020[32] recommends multidisciplinary treatment for LABC with a focus on drug therapy supplemented by surgery and RT. However, in many cases, regular RT fails to achieve satisfactory results for patients with unresectable tumors and many of these patients also do not respond to drug therapy. In this study, we have achieved significant local effects in the treatment of LABC and LRBC with a diameter of 10 cm or larger and open

skin lesions. KORTUC II has improved greatly QOL and has been appreciated by the patients who received this therapy,[15] suggesting it is a highly satisfactory treatment option.

Although the KORTUC II is effective in LC, it requires precautions, as soft tissue necrosis of the chest wall was observed in two patients after treatment. Their common features were that the tumor had invaded deep into the chest wall and the soft tissue necrosis occurred at the same time as the malignant lesions were expanding. The soft tissue necrosis may have been caused by inhibition of normal tissue recovery together with tumor tissue necrosis. Therefore, if imaging shows the tumor is invading deep into the chest wall and the tumor is growing rapidly, it may be best to forego or limit KORTUC II therapy to reduce the risk of soft tissue necrosis. It should be noted that soft tissue necrosis of the chest wall has also been reported with RT alone.[33]

Many fundamental issues remain to be clarified related to KORTUC II, particularly quantified levels of patient benefit and how KORTUC II can be combined optimally with radiation, chemotherapy and immunotherapy to treat various cancers. To date only a single phase 1 clinical trial has been completed, and this showed no significant adverse effects in patients with LABC.[34] Nimalasena et al reported that injection pain was tolerable, dermatitis was not exacerbated, and the tumor regression rate was 50–100%.[34] Biomarker tests demonstrated significant changes in IL-4, MIP-1α, IL-1β, and TRAIL compared with those of the patient group without sensitizer, suggesting apoptosis induced by TNF-related apoptosis-inducing ligands associated with activated T-cell signaling and increased macrophage stimulation.[34] Kariya et al. reported that H2O2 enhanced lysosome-dependent X-ray-induced apoptosis in an *in vitro* experiment.[35] A phase 2 study has been underway in five sites in the United Kingdom since June 2020 – the only phase 2 trial to date. In the future, we need more clinical trials to promote widespread use of KORTUC II and to include it within insurance coverage.

5. Conclusions

KORTUC II demonstrated high rates of LC for LABC and LRBC. These effects may not be achievable with regular RT alone. Moreover, This method can play a major role in alleviating symptoms. KORTUC II is expected to be an inexpensive and extremely promising mode of RT with an excellent radiosensitizing effect.

List Of Abbreviations

Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas (KORTUC)

Locally advanced breast cancer (LABC)

Locally recurrent breast cancer (LRBC).

Maximum tumor shrinkage (MTS)

Loco-regional control (LC)

Progression free survival (PFS)

Time to progression (TTP)

Quality of life (QOL)

Clinical complete response (cCR)

Declarations

Ethics approval and consent to participate

Osaka Medical College Clinical Trials Registry, trial no. 1973, date. May 10, 2010

UMIN Clinical Trials Registry, trial no. UMIN000003734, date. June 10, 2010

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

TS, MN, HY, CS and AH performed KORTUC treatment. TS, and KY analyzed and interpreted the patient data regarding the patients with locally advanced breast cancer or recurrent breast cancer. KK, MI, and KN performed the acquisition, analysis, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Figures

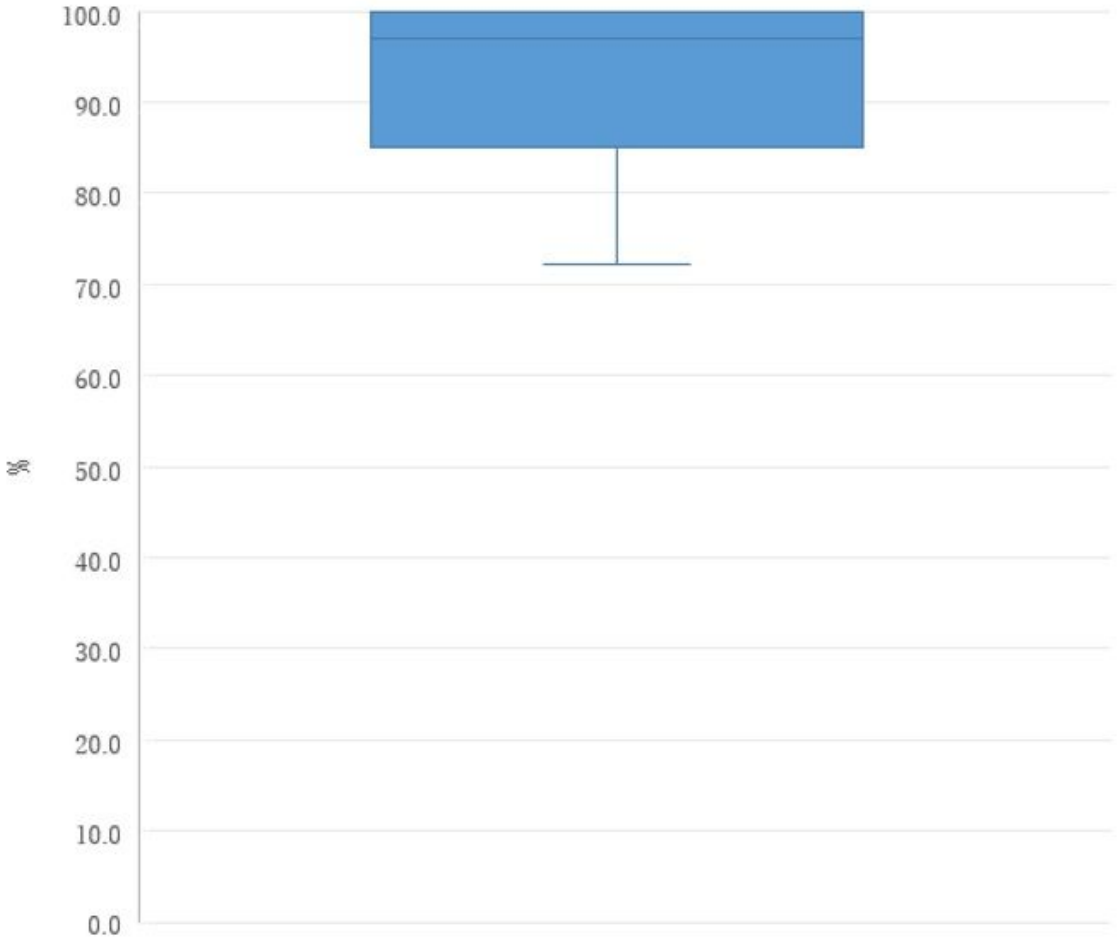

Figure 1

MTS among 30 patients in study. Maximum percent decrease in volume compared to pre-radiation baseline: median 97.0%, mean 91.7% , range 77.2%–100% (standard deviation(SD) = 9.8%)

Figure 2-1

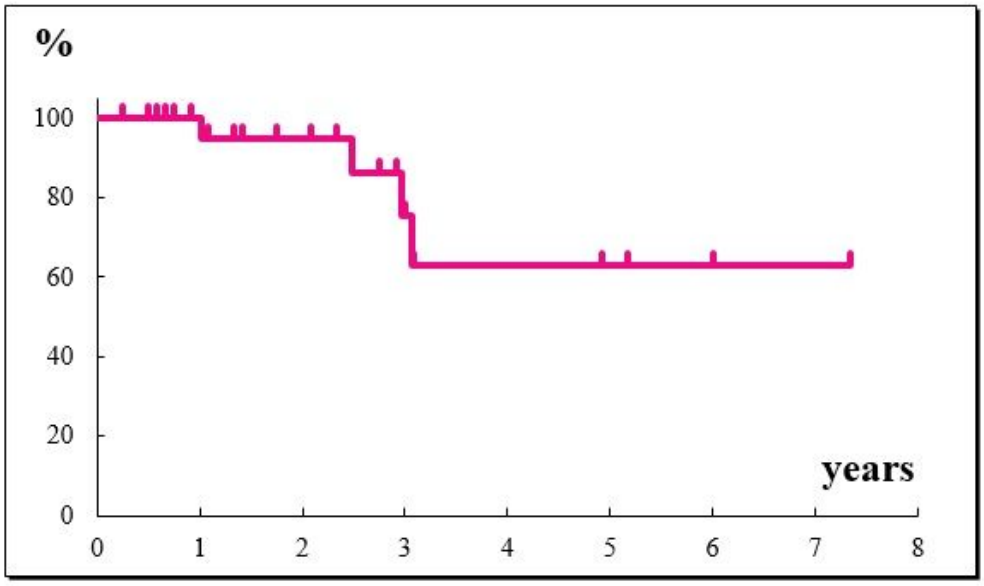

Figure 2-2

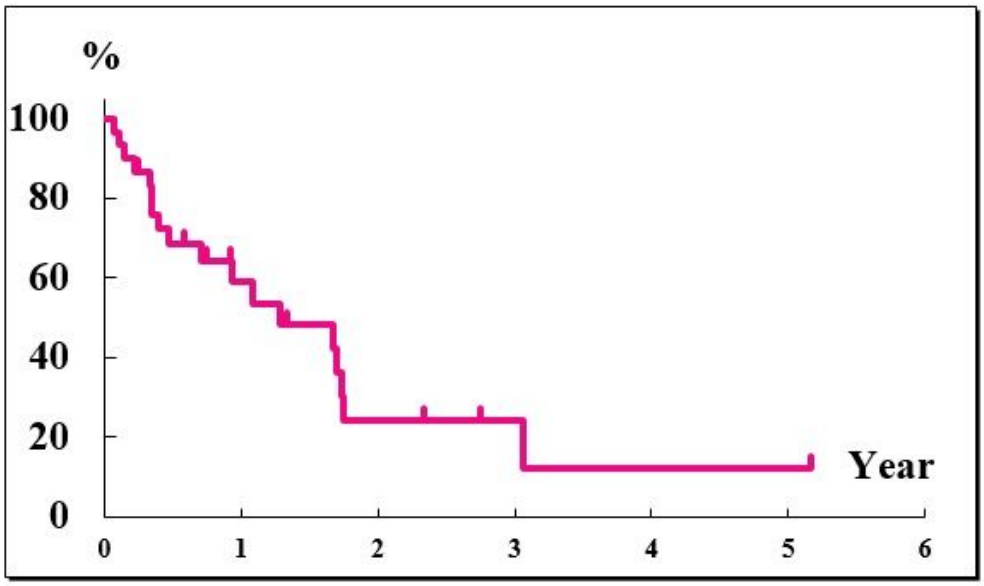

Figure 2

2-1: Kaplan–Meier curve of LC. The local control rates were 100%, 94.7%, and 75.4% at 1, 2, and 3 years, respectively. 2-2: Kaplan–Meier curve of PFS after the completion of RT. Among the 30 subjects, the proportion with PFS were 59%, and 24% of the 30 subjects at 1, and 2 years, respectively.

Figure 3-1

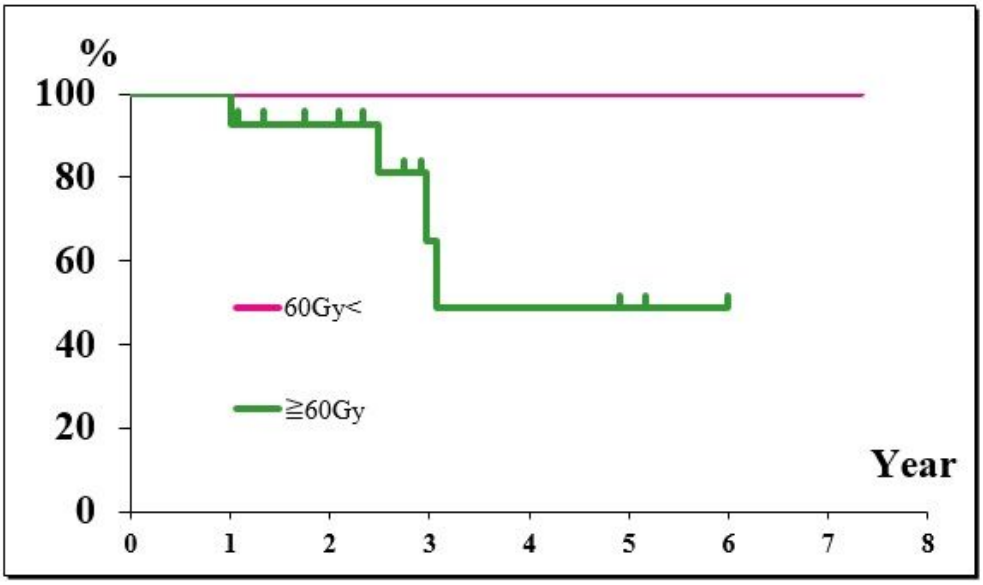

Figure 3-2

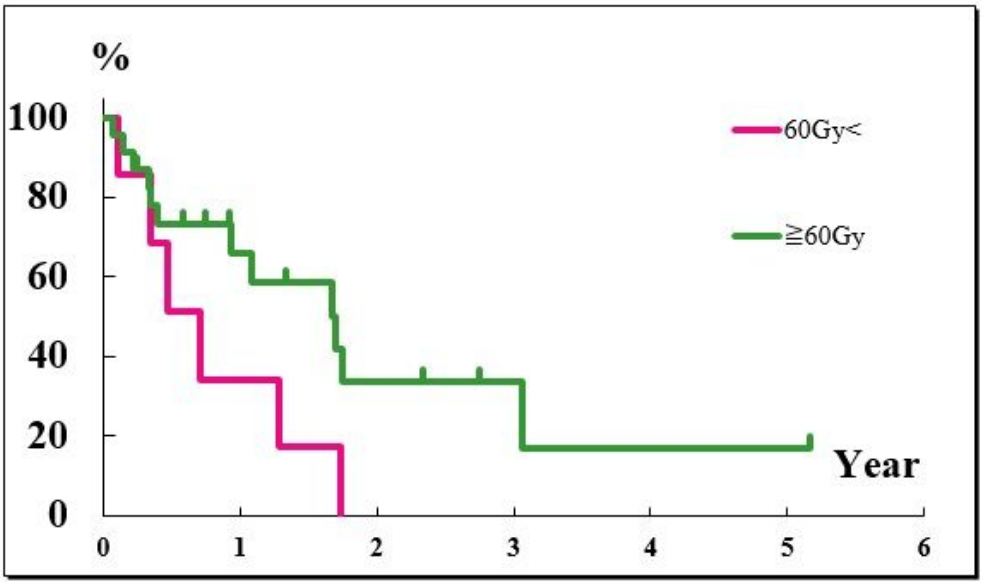

Figure 3

3-1: Kaplan–Meier curve of LC (60Gy< and≧60Gy) Wilcoxon p=0.19 There was no difference in duration of LC between the two groups, 60Gy< and ≧60Gy. 3-2: Kaplan–Meier curve of PFS (60Gy< and≧60Gy) Wilcoxon p=0.21 There was no difference in duration of PFS between the two groups, 60Gy< and ≧60Gy

Figures 4-1 and 4-2 are not available with this version

Figure 4

LC and duration of progression free survival (PFS) after the completion of RT were determined using the Kaplan–Meier method