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Safety and Effectiveness of an Enzyme-Targeting Radiosensitization Agent (KORTUC II) to Treat Uterine Cervical Cancer

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ABSTRACT

Purpose : Local injection into tumors of the low-concentration hydrogen peroxide radiosensitizer agent Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, Type II (KORTUC II) can provide a local sensitizing effect for radiation. Local control is often difficult in patients with bulky or chemoresistant cervical cancer. The purpose of this study was to examine the efficacy and safety of radical radiotherapy with local injection of KORTUC II.

Materials and methods : Nine patients received whole pelvic external beam radiotherapy (EBRT) of 30 Gy in 15 fractions and additional EBRT of 20 Gy in 10 fractions with a central shield. During whole pelvic EBRT, KORTUC II was administered twice a week. Following whole pelvic EBRT, intracavitary brachytherapy (ICBT) of 24 Gy in 4 fractions was prescribed to point A, and KORTUC II was administered concurrently with ICBT.

Results : Of the 9 patients, 5 had bulky tumors and 4 had chemoresistant tumors. All patients were able to receive ICBT and complete the scheduled radiosensitized radiation therapy. The 5-year overall survival rate was 78%, and the actuarial local control rate was 65%. A vesicovaginal fistula developed in 1 patient who had a tumor resistant to chemotherapy.

Conclusion : Local injection of low concentrations of the hydrogen peroxide agent KORTUC II to patients with cervical cancer is a safe radiosensitization method that improves local control.

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Key words : cervical cancer, radiotherapy, radiation sensitizer, hydrogen peroxide, Kochi oxydol-radiation therapy for unresectable carcinomas, Type II

INTRODUCTION

In 2020, uterine cervical cancer was the fourth most common cancer in women worldwide[1] and the fifth most common cancer in Japan[2]. As a radical treatment for locally advanced cervical cancer, radiation therapy is equivalent to surgery. In Japan, where the population is aging, the role of minimally invasive radiation therapy is significant. Owing to good results with definitive radiation therapy, brachytherapy combined with external beam therapy to the pelvic lymph node area has been established as the standard treatment for uterine cervical tumors[3,4]. However, in cases of locally advanced cervical cancer with large tumor volumes, the position of the external uterine orifice is obscured, and inserting the tandem becomes difficult. As a result, the dose of brachytherapy to the cervix often cannot be in-

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creased, leading to a failure of local control. If accurate intracavitary brachytherapy (ICBT) can be performed, cancer of the cervix can be irradiated to a high dose and local control is more likely[5].

In Japan, a standard curative treatment regimen for locally advanced cervical cancer includes 30 Gy in 15 fractions (fr) of whole pelvic irradiation via external beam radiotherapy (EBRT), followed by local irradiation via ICBT to a dose of approximately 24 Gy in 4 fr over 4 weeks to point A. For the pelvic lymph node area, additional irradiation of approximately 20 Gy in 10 fr is performed with a center shield. If EBRT causes the cervical tumor to shrink before the start of ICBT and allows accurate intracavitary irradiation, local control might be more likely. However, the degree of tumor shrinkage with EBRT until the start of ICBT cannot be predicted.

Concomitant chemoradiotherapy has recently improved the overall survival rate of various advanced cancers. The anticancer drugs are believed to suppress systemic metastases and have a local radiosensitizing effect. The effect can be synergistic or additive, but the exact mechanism is unclear[6]. Yasuhiro Ogawa, now a professor emeritus of Kochi University, and his co-workers have shown that cancer tissues, particularly radioresistant cancers and well-differentiated carcinomas, often contain a large amount of antioxidant enzyme peroxidase[7]. Ogawa et al discovered that the radiosesitizing effect was a result of low-concentration hydrogen peroxide deactivating peroxidase in cells and simultaneously decomposing it to generate oxygen[8–10]. The novel radiosensitizer agent Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, Type II (KORTUC II), which contains hydrogen peroxide and sodium hyaluronate, was developed by Ogawa. Theoretically, hypoxic and radioresistant cancer cells become hyperoxic and radiosensitive, with demonstrable therapeutic effects. Ogawa et al. confirmed in clinical trials that the local injection of low-concentration hydrogen peroxide is safe and greatly increases the local effects of radiation [11–13]. Subsequently, an attempt was made to inject low-concentration hydrogen peroxide locally during intraoperative irradiation for the treatment of pancreatic cancer[14].

We have speculated that for patients with locally advanced uterine cervical cancer, accurate intracavitary irradiation after 30.0 Gy of whole pelvic irradiation can enhance local control and reduce late adverse effects. On the basis of their experience of performing brachytherapy for prostate cancer, hospitals are performing interstitial brachytherapy (ISBT) by inserting brachytherapy needles into large tumors of the uterine cervix[15–17]. The ability to safely perform ISBT for cervical cancer suggests that a direct approach to the tumor can be considered safe. Although we cannot perform ISBT at The Jikei University Daisan Hospital, we can insert the tandem and ovoids accurately after EBRT if KORTUC II is administered for cervical cancer by means of ISBT. We believe that this treatment can improve local control and reduce late adverse effects.

The purposes of the present study were to investigate whether KORTUC II can be used to safely and accurately perform ICBT during radical radiotherapy for uterine cervical cancer that is locally advanced or recurrent after chemotherapy and to further confirm whether local control can be achieved.

MATERIALS AND METHODS

1. *Patient selection*

The present study was performed from November 1, 2012, to and November 14, to March 31, 2019, at The Jikei University Daisan Hospital and The Jikei University Hospital, respectively. This study was approved by the Ethics Committee of The Jikei University School of Medicine for Biomedical Research (approval number : 24-180 (6946)) and conducted according to the 1964 Declaration of Helsinki and its later amendments, as well as the Ethical Guidelines for Medical Health Research Involving Human Subjects (2014) by the Japanese Ministry of Health, Labour and Welfare and the Ministry of Education, Culture, Sports, Science and Technology.

Thirty-one patients were enrolled in the study following the provision of written informed consent (Table 1). From these 31 various cancer patients with different treatment intensions, the largest number was 9 patients with cervical cancer : 4 of them were chemoresistanat and 5 of them had bulky tumors. These patients underwent baseline magnetic resonance imaging and intravaginal physical examination to assess the difficulty of ICBT.

2. *Treatment*

A dose of 30 Gy of radiation in 15 fr over 3 weeks was first delivered to the whole pelvis via the 4-field box tech-

Table 1. Number of patients according to primary tumor, and purpose of irradiation

Primary tumor	Lesion of RT	Purpose of RT	Pateints
Malignant meningioma	Metastasis	Palliative	1
Stomach cancer	Metastasis	Palliative	1
Gingiva or oral cancer	Local recurrence	Radical	3
Tongue caner	Metastasis	Palliative	1
Liver cancer	Metastasis	Palliative	3
Breast cancer	Primary	Radical	1
Breast cancer	Local recurrence	Palliative	1
Breast cancer	Metastasis	Palliative	2
Liposarcome	Metastasis	Palliative	1
Renal cancer	Metastasis	Palliative	2
Urothelial cancer	Metastasis	Palliative	1
Lung cancer	Metastasis	Palliative	2
Skin cancer	Local recurrence	Radical	2
Skin cancer	Metastasis	Palliative	1
Uterine cervical cancer	Primary	Radical	9
Total			31

nique and was followed by a dose of 20 Gy in 10 fr over 2 to 3 weeks via an anteroposterior parallel opposed fields with a center shield. During whole pelvic irradiation, KORTUC II was administered through the vagina twice weekly under ultrasonographic guidance before radiotherapy. The agent KORTUC II consists of 0.5 ml of a 3% weight-to-volume ratio (w/v) solution of hydrogen peroxide, 2.5 ml of 1% w/v sodium hyaluronate, and 0.5 ml of 1% lidocaine[18]. For at least 24 hours after the intratumoral injection of KORTUC II the tumor oxygen concentration can be maintained[19], a feature that provides a strong rationale for twice-weekly administration during radiotherapy[12,13,20]. The amount of KORTUC II was adjusted, according to tumor size, from a minimum volume of 1 ml to a maximum volume of 7 ml. (The median amount was 3.5 to 4 ml, although it is not measured exactly to 1 decimal place.)

When intracavitary irradiation was likely to be performed after whole pelvic irradiation, KORTUC II was administered through the cervix along with the inserted ICBT applicator, and high-dose rate brachytherapy was administered remotely with an afterloading system. For ICBT, 6 Gy was administered weekly to point A with a Fletcher-type or Henschke-type applicator. The combination with chemotherapy was not considered to interfere with recognized standard treatment. Several patients received weekly cisplatin.

3. Treatment evaluation

The treatment effect was evaluated after 30.0 Gy of EBRT had been administered by inserting a sonde into the uterus to determine whether ICBT was possible. The final treatment effect was evaluated via pelvic examination 1 or 3 months after the completion of radiation therapy and imaging diagnosis. A reference for determining the effect was the numerical values of the tumor markers (SCC, CEA, and CA125). To evaluate the feasibility of KORTUC II treatment, all treatment-associated complications were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.0)[19].

4. Statistical analysis

The survival model was fitted with data via the Kaplan-Meier method, and differences in the survival rate were assessed with the log-rank test. The software programs used included R programing language version 3.6.2 (R Foundation for Statistical Computing) and Wolfram Mathematica version 12.1.1.0 (Wolfram Research, Inc., Champaign IL, USA).

RESULTS

The comprehensive patient demographics of cervical cancer are summarized in Table 2. These patients were so locally advanced that even with standard ICBT, curative treatment was expected to be difficult.

During whole pelvic irradiation, KORTUC II was injected 3 times in 1 patient, 4 times in 7 patients, and 5 times in 1 patient. Vaginal examination after 30 Gy of whole pelvic irradiation confirmed the external uterine orifice in all patients, suggesting the feasibility of intracavitary irradiation. Overall, the number of KORTUC II injections during ICBT in every patients was 4.

Table 2. Patients characteristics of uterine cervix

Characteristic	Number of patients	Percent
Age (years)		
Median	56	
Range	40–81	
Stage		
IB2	3	33.3%
IIA2	2	22.2%
IIB	1	11.1%
IIIA	1	11.1%
IIIB	1	11.1%
IV	1	11.1%
Pathology		
Squamous cell carcinoma	7	77.8%
Adenocarcinoma	2	22.2%
Chemotherapy		
Induction Chemotherapy	4	44.4%
Concurrent	5	55.6%
KORTUC II		
Pre-intracavitary brachytherapy		
3 times	1	11.1%
4 times	7	77.8%
5 times	1	11.1%
During intracavitary brachytherapy		
4 times	9	100%
External beam radiotherapy		
Whole pelvis dose		
20 Gy	1	11.1%
30 Gy	8	88.9%
Total dose		
50 Gy	6	66.7%
54 Gy	1	11.1%
56 Gy	1	11.1%
60 Gy	1	11.1%

KORTUC II : Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, Type II

All patients received radiation therapy as planned, with a median time to completion of 44 days (range, 40–67 days). The median length of follow-up among surviving patients was 62 months (range : 58–73 months). A total of 3 patients had local failure, and 1 patient underwent salvage surgery and was alive without disease ; therefore, the 5-year actuarial local control rate was 64.8% (Fig. 1a). In addition, the 5-year rate of freedom from distant metastasis was 77.8% (Fig. 1b). Two patients died : 1 from metastatic disease and 1 from another disease. The latter patient, an 81-year-old woman with stage IIa2 squamous cell carcinoma, had completed treatment and was doing well after radiotherapy. However, 18 months later, severe abdominal pain and anemia developed and an endoscopic examination revealed early gastric cancer in a deep benign ulcer. She underwent gastrectomy but 1 month later had severe peritonitis with shock and died. Ultimately, the 5-year disease free survival rate was 53.3% and the overall survival rate was 77.8% (Fig. 1c, d).

Concomitant radiotherapy and chemotherapy with weekly cisplatin was received by 5 patients (55.6%). During the observation period none of the 5 patients who had received concomitant therapy died, but 2 of the 4 patients who had received only radiotherapy died (Fig. 2a) ; however, the overall survival rate did differ significantly between patients who had or had not received concomitant therapy ($p = 0.088$). Disease recurred in 2 of the 5 patients who received concomitant therapy, and disease recurred in 2 of 4 patients who received radiation alone ($p = 0.48$) (Fig. 2b).

A successfully treated patient was a 59-year-old woman with a bulky stage Ib2 squamous cell carcinoma of the cervix who presented with massive genital bleeding (Fig. 3a). Although the external uterine orifice was not apparent due to the bulky tumor, chemoradiotherapy was the treatment of choice. This patient was considered appropriate for the present study ; she agreed to participate after receiving counselling. After the patient received 30 Gy of whole pelvic irradiation in 15 fr and 4 injections of KORTUC II (Fig. 4, 5), the external uterine orifice was identified ; 4 fr of ICBT were delivered (6 Gy to point A at each fraction) with concurrent KORTUC II injections during brachytherapy. After 66 months of follow-up, no recurrence, metastases, or adverse effects were observed (Fig. 3b).

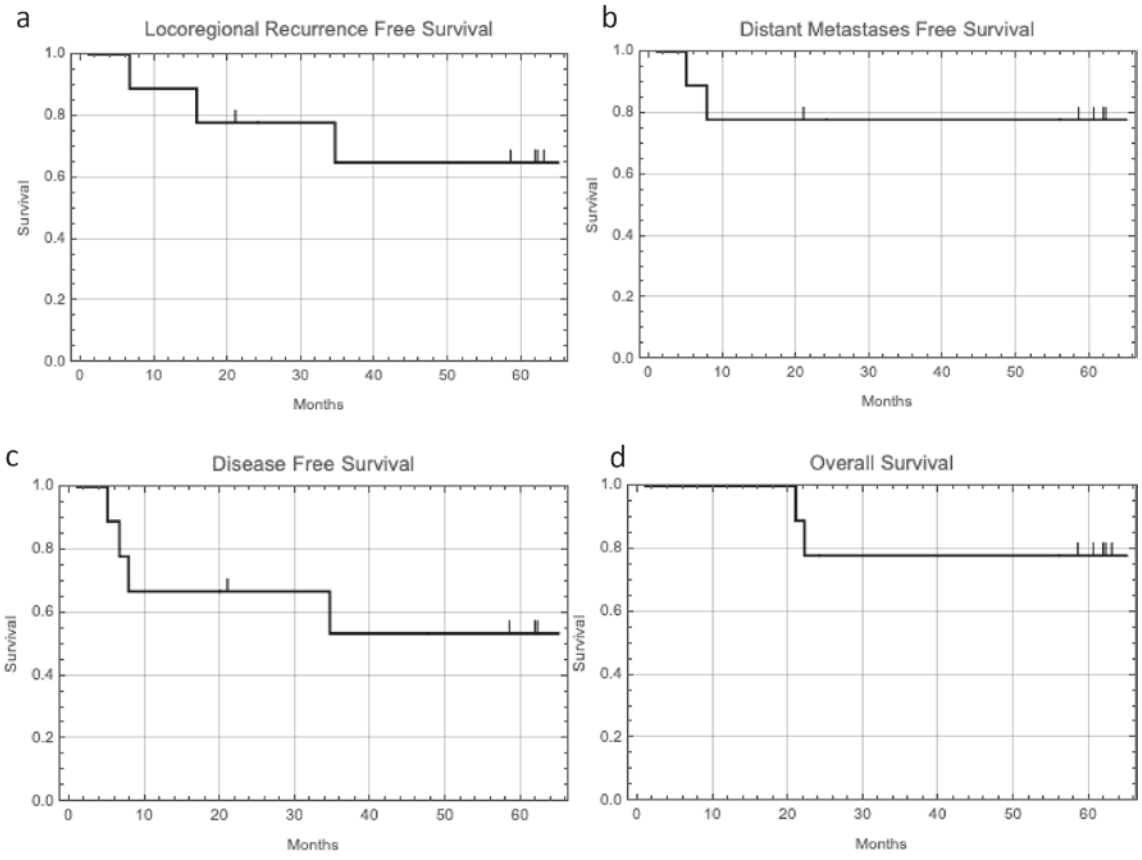

Fig. 1. Rates among patients of (a) locoregional recurrence free survival, (b) distant metastasis free survival, (c) disease free survival, and (d) overall survival at 5 years.

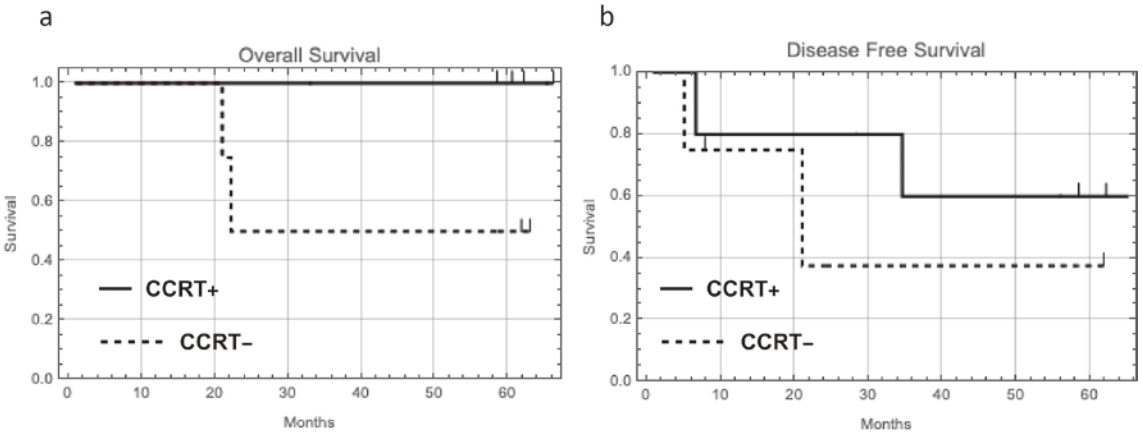

Fig. 2. (a) Overall survival and (b) disease free survival with or without concomitant chemoradiotherapy (CCRT).

Discussion

Patients often undergo radiotherapy to relieve the symptoms of pain or swelling or both caused by the metastasis or recurrence of malignant tumors. Even with radiotherapy, these tumors are likely to be large, resistant to chemotherapy, and difficult to control locally. Table 1 shows the diseases, the purpose of radiotherapy, and the number of patients enrolled in this study. Locally advanced cervical cancer is a good indication for KORTUC II treatment, and a

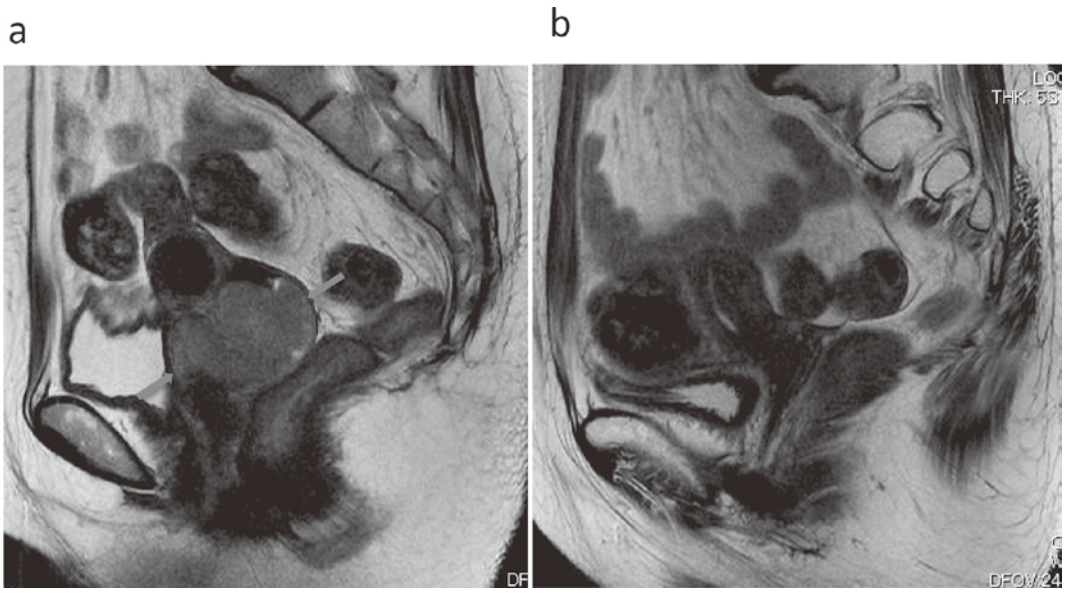

Fig. 3. Therapeutic response following injection of the agent KORTUC II, as evaluated with magnetic resonance imaging examination of the reported patient. (a) T2-weighted magnetic resonance imaging of initial staging workup. Sagittal images shows a cervical mass (arrows). (b) Two months after treatment with KORTUC II ; the cervical mass has almost completely disappeared.

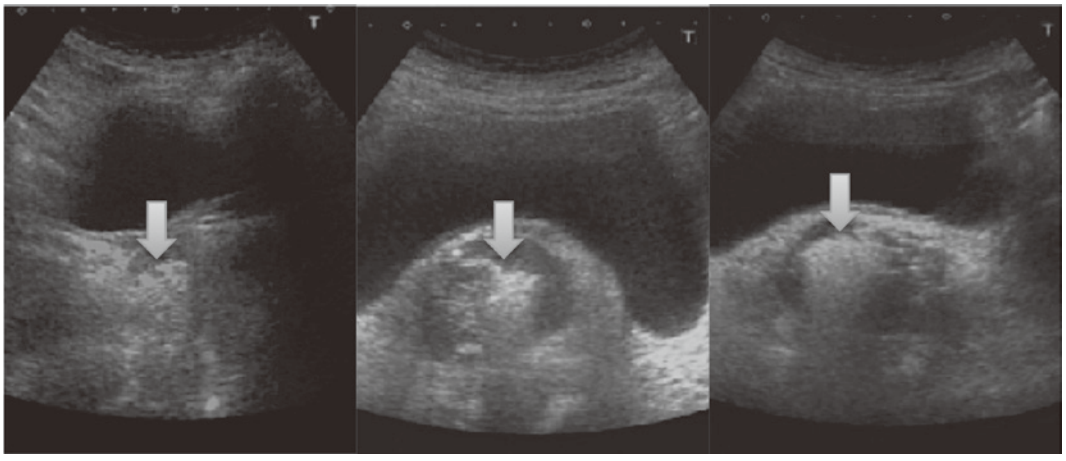

Fig. 4. Ultrasound-guided injection of the agent KORTUC II through a spinal needle (22 gauge, 9 cm) into the tumor. Hyperechoic area spread was induced by the generated oxygen (arrows).

cure is possible if ICBT is properly performed. Therefore, most patients with advanced cervical cancer who were informed about this treatment consented to participate in this clinical study.

Radiation therapy is indicated for uterine cervical cancers of stages I or II with a tumor diameter ≥ 4 cm and of stages III or IV, and concurrent chemotherapy is recommended by the Japan Society of Gynecologic Oncology[21]. However, chemotherapy is not recommended before radiation therapy, as it can be harmful and does not improve the rates of overall survival, disease free survival, local recurrence, and distant metastasis[22,23]. In the present study, 4 (44.4%) of 9 patients received chemotherapy before radiation therapy. Because chemotherapy was performed before surgery and final preoperative evaluation revealed that the local effect of chemotherapy was insufficient, the treatment strategy was changed to radiation therapy. Upon their first visit to the division of Radiotherapy in the department of Radiology, all patients were found to have a large cervical mass, and the external uterine orifice could not be identi-

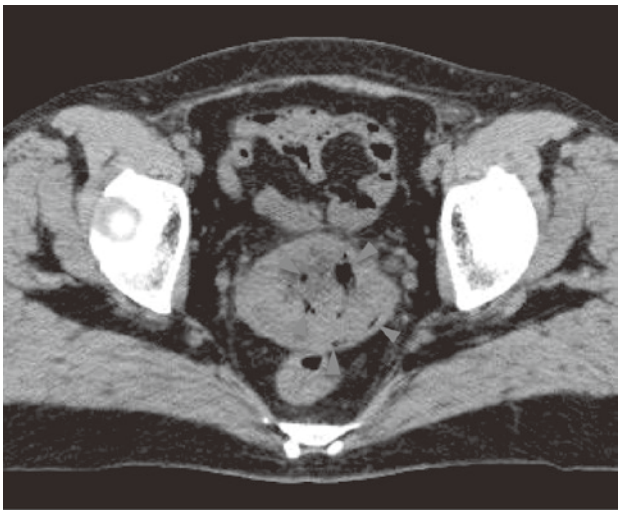

Fig. 5. Computed tomographic image obtained after injection of the agent KORTUC II. Generated oxygen has spread over the tumor, confirmed with air density (arrowheads).

fied. For radical radiotherapy, performing ICBT in combination with EBRT is essential ; proper placement of applicators is important for achieving optimal local control without adverse effects[5]. In a prospective randomized trial, both patients who underwent surgery and patients who underwent radiotherapy had a 5-year overall survival rate of 83% and disease-free survival rate of 74%[24,25]. In the present study, the 5-year survival rate and disease-free survival rate for patients who had a tumor larger than 4 cm were poor if they underwent only surgery or only radiotherapy. Therefore, if the tumor diameter is greater than 4 cm (IB2, IIA2), adjuvant therapy should be considered. In the present study, the combined use of local sensitization therapy via KORTUC II and whole pelvic irradiation was effective in reducing the size of the primary mass and allowing the external uterine orifice to be identified.

The safety of KORTUC II has been shown for patients who have breast cancer, pancreatic cancer, or metastatic lymph nodes[11-14]. In The Jikei University Daisan Hospital, we have administered KORTUC II to patients who have breast cancer or lymph node recurrence of head and neck cancer (Table 1). However, for patients with uterine cervical cancer, the method of administering KORTUC II, its burden on patients, and its safety must be examined. A brachytherapy source has recently been reported to be easily inserted into a uterine cervical tumor with ISBT ; therefore, we believe that KORTUC II can be administered with a fine needle via the vagina[15-17]. However, we explained to patients that twice-weekly administration of KORTUC II during whole pelvic irradiation increases the burden of an additional pelvic examination per week. After KORTUC II was injected, its distribution was assessed with computed tomographic images. Because the computed tomography scanner was in an adjacent room, the burden on the patient was minimal. Moreover, KORTUC II was administered while the intracavitary applicator was inserted during ICBT to ensure that the burden on the patient was minimized.

During ICBT, 6 Gy was administered to point A per fraction. Because brachytherapy offers a steep dose gradient, a high dose exceeding 6 Gy is administered into the tumor near to the radiation source. In an experiment demonstrating the radiosensitizing effect of low-concentration hydrogen peroxide on cancer cells, a single dose of 10 Gy was used[8-10]. Therefore, injection of KORTUC II at the time of ICBT might reflect a similar dose setting to that of cell experiments.

The present study found a 5-year overall survival rate of 78% and a locoregional disease free survival rate of 65%. Such results are considered to be good for patients with tumors that are resistant to chemotherapy and have a diameter > 4 cm[25,26].

Local recurrence was observed in 3 of our patients (30%), but local control was obtained in 1 patient by means of salvage surgery. A vesicovaginal fistula was found in 1 patient, and conservative surgery was required. This patient received 4 courses of chemotherapy (paclitaxel and carboplatin) before undergoing radiation therapy, and anticancer drugs might have been responsible for this adverse effect.

In the present study, we compared the effects of concomitant chemoradiotherapy for cervical cancer with the risk of recurrence or metastasis and the chances of survival ; however, the number of patients was inadequate for detecting a significant difference. Further investigation is, therefore, necessary.

Injection of KORTUC II is a simple and inexpensive radiosensitization method that has been done in the form of clinical study at many institutions after being approved by ethical review committees. However, Japan's New Clinical Trials Act[27], which came into effect in April 2019, has made stricter the ethical examination standards for clinical re-

search on off-label drugs, such as injections of hydrogen peroxide. Because violations of this act can be punished, approval by the ethics committee at each institution before the law takes effect was considered invalid, and this treatment could not be continued. Although KORTUC II was developed in Japan and its use for treatment is expected to continue in the future, there is currently no breakthrough. Researchers interested in the theory of this treatment have begun clinical studies in Europe[20]. We hope that the results will be valid and will be approved in Japan.

CONCLUSION

Low concentration of hydrogen peroxide agent KORYUC II has a sensitizing effect of ionizing radiation on various cancers. Many clinical studies by KORTUC II using this principle have confirmed its effectiveness. In this study, we investigated the safety and efficacy of KORTUC II aginst bulky cervical cancer or cervical cancer that has become resistant to anticancer agents. This treatment is a safe rediosensitization method that improve local control.

Authors have no conflict of interest.

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