KORTUC, a novel hydrogen peroxide-based radiosensitizer for the enhancement of brachytherapy in patients with unresectable recurrent uterine cervical cancer

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Abstract. Kochi Oxydol Radiation Therapy for Unresectable Carcinoma (KORTUC) is a novel radiosensitizer invented by Professor Ogawa at Kochi University (Japan) in 2006. The current study aimed to report the experience of the present authors with the use of KORTUC treatment in combination with interstitial brachytherapy (ISBT), with or without external beam (EB) radiotherapy (RT), in patients with locally recurrent cervical cancer (LRCC), who were likely to have a high risk of poor prognosis. Between April 2012 and January 2020, 14 female patients (15 tumoral lesions) with LRCC underwent KORTUC with ISBT. Their previous treatments included surgery (n=4), radiation therapy (n=8) and surgery plus RT (n=3). The primary lesions were located in the vaginal stump (n=5), pelvic wall (n=3), cervix (n=3), vaginal wall (n=2) and lymph nodes (n=2). At 2 h before RT, KORTUC was injected intratumorally via direct colposcopy. The dose of KORTUC ranged from 4-12 ml, adjusted for the tumor size. For patients who underwent ISBT, KORTUC was administered before and after insertion of the applicator before irradiation. Intratumoral injection of KORTUC was completed without any technical or safety issues in all 15 patients; it was well tolerated with no adverse events observed. KORTUC also showed preferable efficacy; a clinical complete response was observed in 87% of patients and the initial response rate was 100%. The 2-year local control rate in patients who underwent ISBT + KORTUC was 79%, whereas it was 63% in the re-irradiation group which was significantly lower (P=0.02) than that in the non-irradiation group (100%). Based on this finding, KORTUC with external irradiation is considered to be an optimal treatment strategy for patients with newly diagnosed LRCC this disease. Additionally, KORTUC may be an effective radiation response enhancer in multiple cancer types in which locoregional control after RT alone remains poor.

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Introduction

Hypoxia and the simultaneous activation of anti-oxidative enzymes are well-known causes of tumor radio-resistance (1-3). A novel radiosensitizer, Kochi Oxydol Radiation Therapy for Unresectable Carcinoma (KORTUC), was developed by Dr Yasuhiro Ogawa at Kochi University (Japan) in 2006, for the treatment of malignant solid tumors containing numerous hypoxic cancer cells and/or large quantities of antioxidative enzymes (4-6). Hydrogen peroxide (H_2O_2) is the only agent capable of simultaneously inactivating antioxidant enzymes and producing oxygen when applied to tumor tissues (7,8). KORTUC is an injectable radiosensitizing drug solution consisting of 0.5% H_2O_2 and 0.83% sodium hyaluronate (HA). H_2O_2 is the active ingredient in this radiosensitizer, whereas HA sustains H_2O_2 in the tumor and delays the decomposition of H_2O_2, which results in the maintenance of a high concentration of oxygen in the tumor. Injecting these two components at a particular ratio is a key feature of this product. Ogawa *et al* (6) reported that HA was the most effective supporting agent for H_2O_2 in maintaining the oxygen concentration in tumor tissues following intratumoral injection of the H_2O_2 agent and for pain relief at the intratumoral injection site.

A phase 2 clinical trial for locally advanced/recurrent breast cancer is ongoing in the UK and India (NCT03946202). In addition, several clinical studies on various solid tumors are ongoing in Japan (6-11). Clinical research on KORTUC at our institution has been conducted since May 2010; as of April 2023, ~250 patients with various solid cancers received this treatment, including >40 patients with gynecological cancers treated with brachytherapy (BT) and KORTUC.

The present study aimed to report the experience of the present authors with the use of KORTUC, in combination with interstitial BT (ISBT), in patients with locally recurrent cervical cancer (LRCC), who are likely to have a high risk of poor prognosis. Limited studies have evaluated BT for sensitizing gynecological cancers (12,13). Moreover, the present authors have previously reported a case of KORTUC for cervical cancer (14), in which radiotherapy (RT) combined with KORTUC was performed for postoperative pelvic wall recurrence of giant uterine cancer, and long-term control and survival were achieved. Therefore, the present report summarized 15 cases in which ISBT was performed in combination with KORTUC for long-term control and life extension in patients with LRCC localized to the pelvis.

Patients and methods

Ethical considerations. At our institution, KORTUC treatment was performed after written informed consent was obtained from patients who were expected to survive ≥1 year and met the following additional criteria: i) Local control by conventional RT alone was presumed to be difficult; ii) the dosage of additional irradiation they could receive was limited; and iii) patients refused surgery as a treatment option.

Patients with LRCC scheduled to undergo ISBT were enrolled. The present clinical research was approved by the ethics committee of Osaka Medical and Pharmaceutical University [Osaka Medical and Pharmaceutical University; Clinical Trials Registry, trial no. 1973 (May 10, 2010); UMIN Clinical Trials Registry, trial no. UMIN000003734 (June 10, 2010)].

Method for dosing the KORTUC sensitizer. KORTUC is an injectable solution consisting of 0.83% HA and 0.5% H_2O_2 (also known as 'OXYDOL' antimicrobial antiseptic in Japan). It is prepared aseptically before each use by mixing 2.5 ml HA (Adant® Dispo; Meiji Saka Pharma) and 1.0 ml xylocaine 1% with 0.5 ml of OXYDOL to be dispensed as a total volume of 4 ml from a single vial. The dosing volume of KORTUC was 4-12 ml based on the tumor size. When used in combination with external beam RT (EBRT), intratumoral injection of KORTUC was performed either under direct vision via colposcopy or through transrectal ultrasound (TRUS) guidance within 2 h before EBRT. When used in combination with ISBT, KORTUC was administered immediately after the interstitial bapplicator placement. If the treatment was performed for 3 consecutive days or more, KORTUC was additionally injected on the third day of treatment. Applicator implantation was performed under TRUS guidance. The ambulatory implantation technique was used. Flexible needle applicators were cut down shortly to allow the patients to stand up and walk during treatment. Three-dimensional-image CT-based treatment planning with MRI assistance was also performed.

ISBT. For patients with no previous history of irradiation, ISBT was combined with EBRT at 24 or 25 Gy in four or five fractions. For patients with a previous irradiation history, ISBT was administered as monotherapy at 45.5 Gy in seven fractions. For palliative BT, the prescribed dose varies depending on the patient. Local response was assessed by CT/MRI or gynecological examination. The applicators were implanted under TRUS guidance.

Outcomes. Survival periods were measured from the day after the end of treatment. The treatment efficacy was evaluated through gynecological examination, CT and MRI according to RECIST criteria (15).

Statistical analysis. The tumor volume was measured using the Eclipse™ treatment planning system v11.0 (Varian Medical Systems, Inc.). Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as numbers (percentages). The Kaplan-Meier method was used to perform survival analysis and differences were compared using the Wilcoxon rank-sum test. Comparisons between the two groups and differences in the parameters depending on the irradiation dose were performed using the Wilcoxon rank-sum test. All experiments were performed in duplicates. EZR v1.54 (Saitama Medical Center, Jichi Medical University) and Excel 2016 (Microsoft Office Professional Plus 2016; Microsoft Corporation) were used for statistical analyses. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient baseline characteristics. From April 2012 to January 2020, 14 female patients with 15 lesions, with a mean age of 55 years (range, 34-80 years) and primary FIGO stage IIB to IVB with LRCC, received KORTUC in combination with ISBT (Table I).

Tumor site and treatment plans. The previous treatments for the 15 lesions with recurrence were surgery (n=4), radiation therapy (RT; n=8) and surgery + RT (n=3) (Table II). Target lesions included the vaginal stump (n=5), pelvic wall (n=3), cervix (n=3), vaginal wall (n=2) and lymph nodes (n=2). The median tumor volume was 36 ml (range, 5-116 ml). Of the 15 target lesions, four were treated with EBRT and cisplatin-based chemotherapy (weekly cisplatin 40 mg/m^2) before ISBT. The median total BED (EBRT + ISBT) was 75 Gy (range, 54-98 Gy).

Before RT, KORTUC was injected intratumorally under the direct vision of colposcopy. For patients who received ISBT, KORTUC was administered before or after insertion of the applicator, before irradiation. The intratumoral injection of KORTUC was completed without any technical or safety issues for any of the 15 patients. KORTUC was well tolerated and no adverse events related to the KORTUC injection were observed, except for transient local pain (grade 1) in three patients at the injection site. In any of these cases, local pain disappeared within 10 min after injection. No late adverse events such as increased tissue fibrosis associated with the addition of sensitizers were observed. However, in cases where KORTUC was injected before implantation, the transrectal echo image acquired high brightness owing to the influence of oxygen and insertion became difficult because the cross-sectional information was not accessible. Subsequently, in all cases, the injection was performed after implantation and the problem disappeared.

Therapeutic effects. Table III shows that patients were followed up for 6-116 months (median follow-up, 24 months). Of the

Table I. Patients characteristics.

Variable	Total)
Mean age (range), years	55 (34-80)
Histology, n (%)	
Squamous cell carcinoma	11 (73.3)
Adenocarcinoma	4 (26.7)
Primary FIGO stage, n (%)	
IIB	2 (13.3)
IIIA	2 (13.3)
IIIB	9 (60.0)
IVA	2 (13.3)
IVB	2 (13.3)
Prior therapy, n (%)	
RT	8 (53.3)
Surgery	4 (26.7)
Surgery + RT	3 (20.0)

RT, radiation therapy; FIGO, International Federation of Gynaecology and Obstetrics.

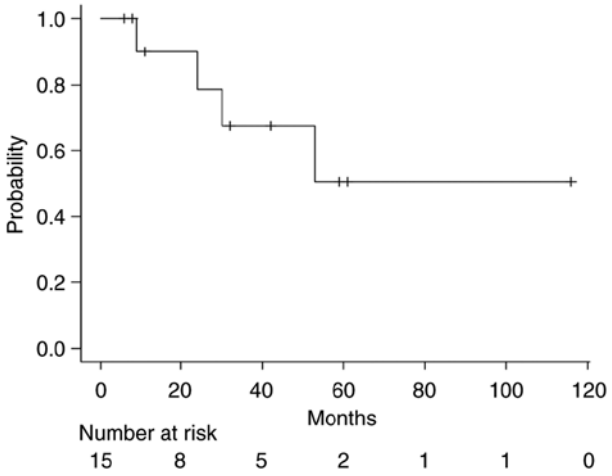

Figure 1. LCR. Median follow-up was 24 months and the 2-year LCR was 79%. LCR, local control rate.

14 patients, eight died due to cancer exacerbation within 8-30 months after treatment. A total of five (33%) patients experienced disease recurrence after treatment. A complete response (CR) was observed in 86.7% (13/15) of patients and the overall response rate (partial response + CR) was 100.0% (15/15).

The 2-year local control rate (LCR) in patients who received ISBT + KORTUC was 79% (Fig. 1). The 2-year LCR was significantly lower (P=0.02) in the re-irradiation group (63%) than that in the non-irradiation group (100%), as shown in Fig. 2.

Discussion

Radical treatment of LRCC is difficult in most cases because several organs located near the tumor site are at risk, such as the rectum, sigmoid colon, small intestine, bladder and

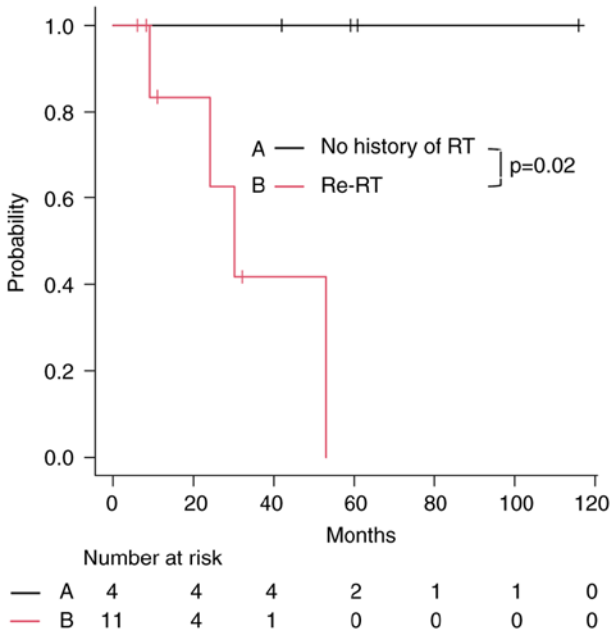

Figure 2. Comparison of LCR with and without a history of irradiation. The 2-year LCR was 100% in patients without a history of RT, whereas it was 63% with a Re-RT. The Re-RT group had a significantly higher recurrence rate than the history of RT group (P=0.02). RT, radiotherapy; LCR, local control rate.

urethra. The indications for curative organ-sparing salvage surgery or pelvic exenteration are limited (16). EBRT with or without chemotherapy is well tolerated; however, its treatment outcomes are not satisfactory and its indication is limited to patients with a history of RT (17). RT has become the treatment of choice for unresectable gynecological cancers (18-20); however, EBRT is almost inapplicable in patients with a history of RT (21).

Therefore, we hypothesize that ISBT may act as a salvage treatment for such patients. However, even in the present case, ISBT (without KORTUC) achieved a 3-year LCR rate of 75% in 56 patients with LRCC (14). The 3-year LCR was 85% in patients with no history of RT after radical surgery, whereas the recurrence rate after radical irradiation was significantly lower (46%) (14). In the present study, the 2-year LCR was 79%, of which 100% was in patients with no history of RT, whereas it was 63% in patients with recurrence and history of RT.

Previous reports indicated that the LCR of ISBT for recurrence after radical irradiation ranges from 45-100% (19-26). This is because, even in the same recurrence cases, there is a mixture of patients with various prognostic factors, such as size, location and previous treatment history; therefore, it is difficult to make a comparison with the present study. The current study did not recruit patients with small tumors close to the vaginal stump that could be controlled with RT alone. For this reason, it was speculated that the results would be lower than those of other studies; nevertheless, good results were obtained in this study.

In agreement with previous studies, KORTUC had almost no adverse events associated with intratumor injection (9-11,27).

However, when KORTUC was injected before implantation, it became difficult to accurately understand the positional

Table II. Patient details regarding RT.

Patient no.	Target lesion	Tumor volume, ml	Post-surgery	Re-RT	External beam radiation therapy, Gy x Fr.	Interstitial brachytherapy, Gy x Fr.	Biological effective dose, α/β10
1	Vaginal stump	69	Yes	No	50/25	24/4	98
2	Vaginal stump	92	No	Yes	ND	45.5/7	75
3	Pelvic wall	116	Yes	No	50/25	25/5	98
4	Ln	5	Yes	No	50/25	21/3	97
5[a]	Vaginal stump	12	Yes	Yes	ND	45.5/7	75
6	Cervix	45	No	Yes	ND	45.5/7	75
7	Ln	11	Yes	No	50/25	18/3	89
8	Pelvic wall	30	No	Yes	ND	45.5/7	75
9	Vaginal wall	7	No	Yes	ND	32.5/5	54
10	Cervix	49	No	Yes	ND	45.5/7	75
11	Vaginal wall	42	No	Yes	ND	40/5	72
12	Pelvic wall	29	No	Yes	ND	25/2	56
13[a]	Vaginal stump	13	Yes	Yes	ND	45.5/7	75
14	Vaginal stump	27	Yes	Yes	ND	45.5/7	75
15	Cervix	83	No	Yes	ND	45.5/7	75

[a]Same patient: No. 13 was treated again when recurrence occurred in no. 5. ND, not determined; Re-RT, re-radiation therapy; Fr, fraction; α/β10: α/β ratio of 10; Ln, lymph node.

Table III. Patients' outcomes.

Patient no.	Local response	Recurrence	Follow-up, months
1	CR	No	116
2	CR	No	11
3	CR	No	61
4	CR	No	59
5[a]	CR	Yes	53
6	PR	Yes	9
7	CR	No	42
8	CR	Yes	24 (TD)
9	CR	Yes	30 (TD)
10	CR	No	6
11	PR	No	8
12	CR	No	8 (TD)
13[a]	CR	No	32
14	CR	No	8
15	CR	N0	6

[a]Same patient: No. 13 was treated again when recurrence occurred in no. 5. CR, complete response, PR, partial response; TD, tumor-related death.

information of the tumor; therefore, this point requires further attention. In this case, the problem can be solved by injection after implantation; however, it becomes somewhat difficult to distinguish between the echo image of the applicator that has already been inserted and the KORTUC injection needle. In CT-guided implantation, the location of the tumor is somewhat obscured; however, information on the position of the injection needle is easy to obtain. MRI-guided implantation has the potential to solve all these problems (tumor and injection needle location information) and the present authors are considering introducing it in the future. At present, it is unclear whether the presence or absence of KORTUC can improve the outcome of RT; however, the current evidence is promising. The present study presents some drawbacks that limit its ability in discussing the efficacy of KORTUC. For example, this study was conducted at a single institution and included a small number of cases. Future studies may evaluate the efficacy of KORTUC by conducting prospective clinical trials at other institutions.

To the best of our knowledge, only one phase I clinical trial has been completed at the time of writing and it showed no significant adverse effects in patients with locally advanced breast cancer (28). A phase II study for breast cancer is ongoing at five sites in the UK and India, which is the only phase II trial to date (NCT03946202). In the future, more clinical trials are needed to promote the widespread use of KORTUC and to include it within insurance coverage. To further evaluate the effects of KORTUC, a Phase I/II study of locally advanced cervical cancer is planned to start in 2023. In that study, KORTUC will be administered in combination with EBRT for newly diagnosed patients with locally advanced cervical cancer.

The present study confirmed that KORTUC intra-tumoral injection is safe, well-tolerated and effective for the ISBT-sensitizing treatment of LRCC. KORTUC also showed efficacy in local control in patients with recurrence. Based on these findings, the present authors would like to confirm in a future study the efficacy of KORTUC combined with EBRT,

as well as ISBT, for newly diagnosed unresectable locally advanced cervical cancer, with high-risk factors of poor prognosis. KORTUC may be an effective radiation response enhancer in multiple cancer types, in which locoregional control after RT alone remains poor.

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Availability of data and materials

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

Authors' contributions

TS, KN and KY designed the study and wrote the manuscript. TS, MN and HY analyzed and interpreted the patient's clinical data. TS, KK, TO, AK, CS, AH and ST performed the KORTUC treatment and statistical analysis. HA contributed to collecting the relevant literature and performing the data analysis. TS and KY 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

Written informed consent was obtained from all patients. Approval was obtained from the Ethics Committee of Osaka Medical and Pharmaceutical University [Osaka Medical and Pharmaceutical University Clinical Trials Registry, trial no. 1973, (May 10, 2010); UMIN Clinical Trials Registry, trial no. UMIN000003734, (June 10, 2010)].

Patient consent for publication

The patients provided written informed consent for the publication.

Competing interests

The authors declare that they have no competing interests.

References

1. Moeller BJ and Dewhirst MW: HIF-1 and tumour radiosensitivity. Br J Cancer 95: 1-5, 2006.
2. Ogawa Y, Nishioka A, Hamada N, Terashima M, Inomata T, Yoshida S, Seguchi H and Kishimoto S: Immunohistochemical study of c-fos-positive lymphocytes infiltrated into human squamous cell carcinomas of the head and neck during radiation therapy and its clinical significance. Clin Cancer Res 3 (12 Pt 1): 2301-2307, 1997.
3. Ogawa Y, Nishioka A, Hamada N, Terashima M, Inomata T, Yoshida S, Seguchi H and Kishimoto S: Expression of Fas (CDcd95/APO-1) antigen induced by radiation therapy for diffuse B-cell lymphoma: Immunohistochemical study. Clin Cancer Res 3 (12 Pt 1): 2211-2216, 1997.
4. Ogawa Y, Kubota K, Ue H and Nishioka A: Development and clinical application of a new radiosensitizer containing hydrogen peroxide and hyaluronic acid sodium for topical tumor injection-A new enzyme-targeting radiosensitization treatment, KORTUC II (Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, Type II). In: Procedings of the 8th International Meeting on Progress in Radio-Oncology (ICRO/OGRO 8). ICRO/OGRO 8 183: 100-101, 2007.
5. Ogawa Y, Ue H, Tsuzuki K, Tadokoro M, Miyatake K, Sasaki T, Yokota N, Hamada N, Kariya S, Hitomi J, *et al*: New radiosensitization treatment (KORTUC I) using hydrogen peroxide solution soaked gauze bolus for unresectable and superficially exposed neoplasms. Oncol Rep 19: 1389-1394, 2008.
6. Ogawa Y, Kubota K, Ue H, Kataoka Y, Tadokoro M, Miyatake K, Tsuzuki K, Yamanishi T, Itoh S, Hitomi J, *et al*: Phase I study of a new radiosensitizer containing hydrogen peroxide and sodium hyaluronate for topical tumor injection: A new enzyme targeting radiosensitization treatment, Kochi Oxydol Radiation Therapy for Unresectable Carcinomas, type II (KORTUC II). Int J Oncol 34: 609-618, 2009.
7. Ogawa Y, Kubota K, Aoyama N, Yamanishi T, Kariya S, Hamada N, Nogami M, Nishioka A, Onogawa M and Miyamura M: Non-surgical breast-conserving treatment (KORTUC-BCT) using a new radio-sensitization method (KORTUC II) for patients with stage I or II breast cancer. Cancers (Basel) 7: 2277-2289, 2015.
8. Takaoka T, Shibamoto Y, Matsuo M, Sugie C, Murai T, Ogawa Y, Miyakawa A, Manabe Y, Kondo T, Nakajima K, *et al*: Biological effects of hydrogen peroxide administered intratumorally with or without irradiation in murine tumors. Cancer Sci 108: 1787-1792, 2017.
9. Shimbo T, Nakata M, Yoshioka H, Sato C, Hori A, Kimura K, Iwamoto M, Yoshida K, Uesugi Y, Akiyama H and Nihei K: New enzyme-targeting radiosensitizer (KORTUC II) treatment for locally advanced or recurrent breast cancer. Mol Clin Oncol 15: 241, 2021.
10. Obata S, Ishimaru Y, Miyagi S, Nakatake M, Kuroiwa A, Ohta Y, Kan T, Kanegae S, Inoue Y, Nishizato R and Miyazaki K: Actual practice of Kochi oxydol radiation therapy for unresectable carcinomas by intra-tumoral administration of hydrogen peroxide as a radiosensitizer. Mol Clin Oncol 16: 68, 2022.
11. Nishioka A, Ogawa Y, Miyatake K, Tadokoro M, Nogami M, Hamada N, Kubota K, Kariya S, Kohsaki T, Saibara T, *et al*: Safety and efficacy of image-guided enzyme-targeting radiosensitization and intraoperative radiotherapy for locally advanced unresectable pancreatic cancer. Oncol Lett 8: 404-408, 2014.
12. Tseng M, Ngoi NY, Tan DS and Tong PS: Combined modality management of advanced cervical cancer including novel sensitizers. Int J Gynecol Cancer 32: 246-259, 2022.
13. Zhou Y, Espenel S, Achkar S, Leary A, Gouy S and Chargari C: Combined modality including novel sensitizers in gynecological cancers. Int J Gynecol Cancer 32: 389-401, 2022.
14. Nakata M, Yoshida K, Shimbo T, Yoshikawa N, Yoshioka H, Hori A, Sato C, Uesugi Y, Kogata Y, Masui K, *et al*: High-dose-rate interstitial brachytherapy with hypoxic radiosensitizer KORTUC II for unresectable pelvic sidewall recurrence of uterine cervical cancer: A case report. J Contemp Brachytherapy 12: 606-611, 2020.
15. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
16. Miller B, Morris M, Rutledge F, Mitchell MF, Atkinson EN, Burke TW and Wharton JT: Aborted exenterative procedures in recurrent cervical cancer. Gynecol Oncol 50: 94-99, 1993.
17. Maneo A, Landoni F, Cormio G, Colombo A, Placa F, Pellegrino A and Mangioni C: Concurrent carboplatin/5-fluorouracil and radiotherapy for recurrent cervical carcinoma. Ann Oncol 10: 803-807, 1999.
18. Stock RG, Chan K, Terk M, Dewyngaert JK, Stone NN and Dottino P: A new technique for performing Syed-Neblett template interstitial implants for gynecologic malignancies using transrectal-ultrasound guidance. Int J Radiat Oncol Biol Phys 37: 819-825, 1997.
19. Mabuchi S, Takahashi R, Isohashi F, Yokoi T, Okazawa M, Sasano T, Maruoka S, Anzai M, Yoshioka Y, Ogawa K and Kimura T: Reirradiation using highdose-rate interstitial brachytherapy for locally recurrent cervical cancer. Int J Gynecol Cancer 24: 141-148, 2014.

20. Nag S, Yacoub S, Copeland LJ and Fowler JM: Interstitial brachytherapy for salvage treatment of vaginal recurrences in previously unirradiated endometrial cancer patients. Int J Radiat Oncol Biol Phys 54: 1153-1159, 2002.
21. Hedman M, Bjork-Eriksson T, Mercke C, West C, Hesselius P and Brodin O: Comparison of predicted and clinical response to radiotherapy: A radiobiology modelling study. Acta Oncol 48: 584-590, 2009.
22. Yoshida K, Yamazaki H, Kotsuma T, Takenaka T, Masui K, Yoshioka Y, Uesugi Y, Shimbo T, Yoshikawa N, Yoshioka H, *et al*: Treatment results of image-guided high-dose-rate interstitial brachytherapy for pelvic recurrence of uterine cancer. Brachytherapy 14: 440-448, 2015.
23. Viswanathan AN, Cormack R, Holloway CL, Tanaka C, O'Farrell D, Devlin PM and Tempany C: Magnetic resonance-guided interstitial therapy for vaginal recurrence of endometrial cancer. Int J Radiat Oncol Biol Phys 66: 91-99, 2006.
24. Beriwal S, Rwigema JC, Higgins E, Kim H, Houser C, Sukumvanich P, Olawaiye A, Richard S, Kelley JL, Edwards RP and Krivak TC: Three-dimensional imagebased high-dose-rate interstitial brachytherapy for vaginal cancer. Brachytherapy 11: 176-180, 2012.
25. Popowski Y, Hiltbrand E, Joliat D and Rouzaud M: Open magnetic resonance imaging using titanium-zirconium needles: Improved accuracy for interstitial brachytherapy implants? Int J Radiat Oncol Biol Phys 47: 759-765, 2000.
26. Tewari K, Cappuccini F, Brewster WR, DiSaia PJ, Berman ML, Manetta A, Puthawala A, Nisar Syed AM and Kohler MF: Interstitial brachytherapy for vaginal recurrences of endometrial carcinoma. Gynecol Oncol 74: 416-422, 1999.
27. Ogawa Y, Kubota K, Ue H, Tadokoro M, Matsui R, Yamanishi T, Hamada N, Kariya S, Nishioka A, Nakajima H, *et al*: Safety and effectiveness of a new enzyme-targeting radio-sensitization treatment (KORTUC II) for intratumoral injection for low-LET radio-resistant tumors. Int J Oncol 39: 553-560, 2011.
28. Nimalasena S, Gothard L, Anbalagan S, Allen S, Sinnett V, Mohammed K, Kothari G, Musallam A, Lucy C, Yu S, *et al*: Intratumoral hydrogen peroxide with radiation therapy in locally advanced breast cancer: Results from a phase 1 clinical trial. Int J Rad Oncol Biol Phys 108: 1019-1029, 2020.