SPANDIDOS PUBLICATIONS

MOLECULAR AND CLINICAL ONCOLOGY 15: 142, 2021

Radiosensitization using hydrogen peroxide in patients with cervical cancer

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Received October 16, 2020; Accepted March 9, 2021

DOI: 10.3892/mco.2021.2304

Abstract. The purpose of the present study was to analyze the feasibility and safety of radiosensitization using hydrogen peroxide for cervical cancer. In superficial tumors, breast cancer and hepatocellular carcinoma, the safety and effectiveness of radiosensitization has been reported; to the best of our knowledge, however, there are no reports on cervical cancer. A total of 20 patients with cervical cancer were recruited. Inclusion criteria were as follows: Patients who required radical external beam radiotherapy (RT); ineligible for or refused brachytherapy; age, ≥20 years; no hematogenous metastasis; Eastern Cooperative Oncology Group Performance Status up to 2; and had not undergone prior treatment. Hydrogen peroxide was used twice a week in combination with RT. A 3% hydrogen peroxide solution-soaked gauze was inserted into the vagina during RT. A total of 45 Gy was delivered in 25 fractions to the whole pelvis with a boost of 10 Gy in 5 fractions if pelvic or para-aortic metastatic lymph nodes were observed. Ultimately, 18 patients were evaluated. Among the 17 patients (excluding one patient with tumor *in situ)*, the one- and two-year overall survival rates were both 90% in patients with stage I/II and 86% in stage III/IV cervical cancer. The adverse events were well tolerated with no severe acute or late adverse events. Although limited by small sample size, short observation time and low radiation dose, the present study demonstrated that radiosensitization treatment may be an option for patients who cannot undergo brachytherapy. The study was retrospectively registered at the university hospital medical information network center (no. UMIN000039045) on January 6, 2020.

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Abbreviations: RT, radiotherapy; ROS, reactive oxygen species; O_2-, superoxide anion; HO, hydroxyl radical; LET, linear energy transfer; CT, computed tomography; LN, lymph node; CR, complete response; PD, progressive disease; SD, stable disease; OS, overall survival; PFS, progression-free survival rate; EBRB, external-beam RT boost

Key words: radiosensitization, hydrogen peroxide, cervical cancer, tumor hypoxia

Introduction

Tumor hypoxia is a major constraint in the use of radiotherapy (RT) and numerous types of chemotherapy, such as alkylating agents, carboplatin and anthracyclines (1). Various pathogenetic mechanisms contribute to the development of hypoxia in solid tumors. Hypoxia is associated with malignant progression, increased tumor invasion, angiogenesis, and increased metastasis formation (2). Reactive oxygen species (ROS), including free radicals, such as superoxide anions (O_2-) and hydroxyl radicals (HO) and non-radical species such as H_2O_2, are effective molecules in RT, contributing to RT-induced DNA damage and cancer cell death. Enhancing ROS production by various means has been investigated as a radiosensitizing strategy (3). Ogawa (4) studied the effect of tumors irradiated in the presence of hydrogen peroxide and found that the activity of anti-oxidative enzymes, such as peroxidase and catalase, were blocked while oxygen molecules were simultaneously produced via the H_2O_2 effect, in which H_2O_2 produced by reactive oxygen species accumulates in the cytoplasm and then moves into the lysosomes, where it causes lysosomal membrane dysfunction and ultimately apoptosis, resulting in oxidative damage to low-linear energy transfer (LET)-radioresistant tumor cells, thereby rendering them highly sensitive to irradiation. UK reseachers to aimed to confirm the safey and efficacy of Kochi Oxydol Radiation Therapy for Unresectable Carcinomas (KORTUC) in breast cancer. Nimalasena *et al* (5) conducted a Phase I clincal trial, which involved 12 patients with locally advanced breast cancer, and demonstrated the safety and tolerability of intravaginal H_2O_2 + external beam RT; a Phase II control arm trial by the same UK group is starting now (6).

There were 604,127 new cervical cancer cases reported worldwide in 2020, which made cervical cancer the fourth most common cancer among women globally (7). External RT combined with brachytherapy and chemotherapy is the standard treatment for cervical cancer (8). Brachytherapy involves the application of a radioactive source in close proximity to the tumor. It takes advantage of the inverse-square law whereby

the RT dose is inversely proportional to the square of the distance from the source, allowing for a high dose to the tumor with relative sparing of the surrounding normal structure. Brachytherapy is the only demonstrated method of providing a high dose required to control cervical cancer without causing severe side effects (9).

In Japan, the delivery of treatment to patients with cervical cancer is complicated by various obstacles. Among 897 radiation oncology facilities, only 163 (18%) are equipped with brachytherapy; of those, only 150 (17% of all facilities) have a machine in use (10). Moreover, because brachytherapy procedures are uncomfortable, certain patients refuse this treatment. In order to address this problem and in light of prior work by Ogawa *et al* (11,16), the present study sought to analyze the feasibility and safety of radiosensitization using hydrogen peroxide as a substitute for brachytherapy for the treatment of cervical cancer.

Materials and methods

Under the Juntendo Urayasu Hospital's review board approval, patients with cervical caner requiring radiosensitization treatment due to an inability to undergo standard therapy were recruited from Juntendo Urayasu Hospital between February 2014 and August 2019. Eligible patients had cervical cancer of any pathology; required RT; were ineligible for or refused brachytherapy; aged ≥20 years; were without hematogenous metastasis; had an Eastern Cooperative Oncology Group Performance Status up to 2; and had not undergone prior treatment. No restrictions were imposed regarding the use or type of concomitant chemotherapy. Patients who met the study criteria were examined, the therapy was explained and, for the patients who refused brachytherpy, it was emphasized that brachytehrapy was the most suitable method and that the survival rates of using external irradiation alone are worse than those of combination brachytherapy. After ensuring full understanding and obtaining written informed consent, participants were enrolled in the study. Treatment planning was performed on a Pinnacle 3 treatment planning system (Philips Medicals Systems, Inc.) with computed tomography (CT) imaging (GE High Speed; GE Healthcare Japan). Patients began treatment two working days after CT imaging. The clinical target volume was created by contouring the uterus, proximal vagina, paracervical and parametrial tissue, including uterosacral ligaments, and pelvic nodal basins. If positive lymph nodes (LN) were detected in the common iliac node or fare above, para-aortic nodal basins were also contoured. The planning target volume incorporated an additional 5 mm set up margin to the clinical target volume.

Hydrogen peroxide was used twice per week (Monday and Thursday or Tuesday and Friday) in combination with RT. Radiosensitization treatment was performed only twice per week because mucous membranes are more sensitive to X-rays than skin (17), so a relatively low frequency was selected to avoid severe adverse events. Immediately before RT, a gauze soaked in 3% hydrogen peroxide solution was inserted into the vagina, ensuring firm contact with the lesion. The gauze was removed immediately following RT. The gauze was intended to be inserted only for the duration of treatment (~10 min). However, because the Gynecology Department is 10 min walk from the Department of Radiation Oncology, the gauze typically remained inserted for 20-30 min. The procedure was performed by the attending gynecologist. The RT dose was 45 Gy over 25 fractions delivered to the whole pelvis from four directions using 10-MV X-rays from a linear accelerator (Elekta Synergy Platform; Elekta Instrument AB) five days per week. For pelvic metastatic LN, a boost of 10 Gy was delivered in 5 fractions. The moderate total RT dose was selected in consideration of potential salvage surgery in case of residual tumor following RT. In case of metastatic para-aortic LN but absent distant metastases, the para-aoritic area was included within the first treatment field and a 10 Gy boost was delivered.

The primary objective was to assess the safety and toxic effects of radiosensitization with hydrogen peroxide. The dose limiting toxicity was grade three or worse vaginal mucositis. Secondary objectives for the present study included locoregional control after one month, progression-free survival (PFS) and overall survival (OS).

Acute and late adverse events were evaluated at one and six months after completion of RT, as per the Common Terminology Criteria for Adverse Events, Version 4.0 (18). Efficacy of the treatment was evaluated in reference to Response Evaluation Criteria in Solid Tumours (RECIST) (19). In brief, complete response (CR) was defined as disappearance of target lesions, partial response was defined as ≥30% decrease in the sum of diameters of target lesions and progressive disease (PD) was definced as ≥20% increase in the sum of diameters of target lesions. Any other response was defined as stable disease (SD). Evaluation was performed by comparing CT and magnetic resonance images and pelvic examination findings before and 1-3 months after completion of RT.

Results

Reasons for selecting radiosensitization treatment over brachytherapy included severe congenital hip joint dislocation precluding the use of brachytherapy (n=2), huge tumor size (n=1) and refusal of brachytherapy (n=15). Because there is no brachytherapy facility within Juntendo University Urayasu Hospital, patients must travel >1 h to the nearest hospital to undergo brachytherapy. Since adverse events due to chemotherapy and RT are expected (20), many patients experience anxiety about such travel and refuse brachytherapy.

A total of 20 patients met the inclusion criteria. Of these, one received only once-per-week gauze insertion due to a protocol deviation. One patient discontinued treatment after two radiosensitization treatments due to overall poor health and died soon after. This was a 78-year-old patient with small cell cancer. At admission, she exhibited para-aortic LN metastasis (stage IVB) but was near full ambulatory (performance status 1). However, tumor progression was rapid and on the second day of radiation she developed bilateral hydronephrosis. On the third day of radiation, a percutaneous nephrostomy was placed in the bilateral kidney. Over the weekend, she developed a high fever due to a urinary tract infection. On Monday (day 5 of radiation), her blood pressure dropped; gauze insertion was stopped but irradiation was continued to decrease the size of the tumor. Radiation was stopped on day 7 because she was in critical condition. She died nine days later. This patient had received gauze insertion twice and 7 fractions of 1.8 Gy

to the whole pelvis and para-aorta. One patient switched to brachytherapy following three radiosensitization treatments owing to a change of mind. Two patients who discontinuted treatment were excluded. Regarding concurrent chemotherapy, 14 patients received cisplatin, two received 5-fluorouracil and two underwent no chemotherapy (one of whom had early stage disease, while the other had kidney dysfuction).

As a result, 18 patients were included in the analysis (mean age, 64.5 years; range, 37-83 years). The stage distribution was as follows: Tumor *in situ*, 1; stage IB, 2; IIA, 2; IIB, 6; IIIB, 2 and IVB, 5. Of these 18 patients, 4 had pelvic LN metastases (22%) and 3 had both pelvic and para-aortic LN metastases (17%). Patient characteristics are summarized in Table I. Treatments are summarized in Tables II and III provides a summary of individual patient outcomes.

Outcomes were evaluated one month after completion of treatment. Overall, 15 patients achieved CR (83%) and three achieved PR (17%). Of those achieving CR, five experienced pelvic recurrence at 6, 12,13,16 and 18 months after completing RT (of these, three had pelvic LN metastases before treatment); all three patients who achieved PR exhibited disease progression and mortality due to distant metastases or severe cachexia at 4, 8 and 23 months after RT completion (of these, one had pelvic metastasis before treatment). The remaining ten maintained CR at the time of analysis. The one- and two-year PFS was 69.0 and 55.2% and the one- and two- year OS was 81.6 and 68.0%, respectively.

Among the five CR patients who experienced local (pelvic) recurrence, cervical tumor size was >50 mm (mean maximum diameter, 62 mm). In comparison, of the ten CR patients who showed no sign of recurrence by the end of the study, only four had tumors >50 mm in size (mean maximum diameter, 44 mm; Table III).

The acute and late adverse events are summarized in Table IV. The adverse events included diarrhea, mucositis, nausea, neutropenia, anemia and thrombocytopenia. Treatment was well tolerated with no acute Grade 3 or worse mucositis due to gauze insertion. A total of 15 patients whose follow-up exceeded 6 months,including one who died at 10 months, (median, 28 months) were evaluated for late adverse events. No notable late adverse events had been observed by the end of analysis.

Table I. Patient (n=18) and tumor characteristics.

Characteristic	Number of patients
Pathology	
Squamous cell carcinoma	14
Adenocarcinoma	2
Adenosquamous carcinoma	2
Stage	
I	2
II	8
III	2
IV	5
Tumor *in situ*	1
Performance status	
0	17
1	1

Table II. Treatment administered to patients (n=18).

Treatment method	Number of patients
Pelvic irradiation only	10
Boost to LN only	4
Para-aortic LN irradiation only	0
Boost + para-aotic LN irradiation	4
Concomitant chemotherapy	
Cisplatin	14
5-fluorouracil	2
No chemotherapy	2

LN, lymph node.

Discussion

In 2008, to improve the effect of low-LET RT, Ogawa *et al* (11) developed a novel radiosensitization treatment called KORTUC, which uses a 3% w/v hydrogen peroxide solution-soaked gauze for superficially exposed and unresectable neoplasms, such as malignant melanoma and malignant fibrous histiocytoma. They analyzed five patients who received 48 Gy over 12 fractions three times per week. Two patients showed CR and the remaining three experienced PR without severe complications. In 2011, Ogawa *et al* developed a novel radiosensitizer for intratumoral injection called KORTUC II, comprising a combination of hydrogen peroxide and sodium hyaluronate. A total of 52 patients with unresectable or recurrent neoplasms were enrolled and followed for at least a year. No patients experienced severe adverse effects. RECIST-determined CR and PR rates were 57 and 26%, respectively and one-year survival was 74% (12). In 2016, Aoyama *et al* (13) reported a follow-up study of 20 patients with recurrent breast cancer from the aforementioned cohort. The total dose was 44.00-49.50 Gy (X-ray irradiation) or 40.00-48.00 Gy (electron beam irradiation). Of the 24 lesions presented by the 20 patients, 18 exhibited CR, 5 exhibited PR, 0 was SD and 1 was PD. The one- and two-year OS rates were 100 and 95%, respectively. In 2017, Aoyama *et al* (14) reported a follow up study of seven patients with unresectable breast cancer from the aforementioned cohort. The total RT dose was 44.0-49.5 Gy over 16-18 fractions. Injection was initiated from the sixth RT fraction and was performed twice per week. The OS was 100 and 86% at one and two years post-treatment, respectively.

In 2014, treatment with an injection of hydrogen peroxide and sodium hyaluronate into a tumor immediately prior to intraoperative RT was tested in patients with stage IVA locally advanced unresectable pancreatic cancer followed by externalbeam RT and systemic chemotherapy (15). The one- and two-year survival rates for the 12 patients in this analysis were 75 and 25%, respectively. There were no serious complications. A retrospective study (16) investigated 72 patients with stage I-II breast cancer who received

Table III. Summary of individual patient outcomes.

Patient	Age, years	Stage	Pathology	Mean maximun diameter, mm	Outcome	Follow-up period, months	Recurrence period, months	Recurrence site
1	80	Tis	SCC	0	CR	25	N/A	N/A
2	72	IB	SCC	33	CR	32	N/A	N/A
3	37	IB	SCC	40	CR	41	N/A	N/A
4	83	IIA	SCC	27	CR	57	N/A	N/A
5	75	IIA	SCC	70	CR	48	N/A	N/A
6	71	IIB	ADE	55	PR→ PD (mortality)	10 (mortality)	4	Lung
7	54	IIB	SCC	60	CR	32	N/A	N/A
8	58	IIB	SCC	50	CR→ Recurrence	25 (mortality)	18	Vagina
9	40	IIB	SCC	78	PR→ PD	24 (mortality)	1	Iliac LN
10	70	IIB	SCC	50	CR→ Recurrence	25	6	Iliac LN and sacral bone
11	64	IIB	SCC	80	CR	24	N/A	N/A
12	65	IIIB	SCC	60	CR→ Recurrence	26	12	Bladder
13	66	IIIB	SCC	42	CR	24	N/A	N/A
14	62	IVA	SCC	51	CR→ Recurrence	31	13	Cervix
15	68	IVA	SCC	52	CR→ Recurrence	30	16	Groin LN
16	42	IVA	ADSQ	75	PR→ PD	5 (mortality)	3	Peritoneum and pelvic LN
17	44	IVA	ADE	40	CR	33	N/A	N/A
18	54	IVA	ADSQ	30	CR	24	N/A	N/A

Patient 4 only once-per-week gauze insertion due to a protocol mistake. Tis, tumor *in situ*; SCC, squamous cell carcinoma; ADE, adenocarcinoma; ADSQ, adenosquamous carcinoma; CR, complete response; PR, partial response; PD, progressive disease; N/A, not applicable; LN, lymph node.

KORTUC II treatment between 2006 and 2014. The total RT dose was 44 Gy over 16 fractions followed by electron boost of 3 Gy three times. The 5-year OS, PFS and local control rates were 100.0, 97.1 and 97.1%, respectively.

External-beam RT combined with brachytherapy and chemotherapy is the standard treatment for stage IB2-IVA cervical cancer (8). In Japan, because of the lack of brachytherapy facilities (10), patients must travel to a remote hospital during RT or forego brachytherapy altogether. The situation is particulary challenging in resource-limited countries: It has been reported that only 20 of 52 African countries provided brachytherapy in 2010 and only nine centers in Latin America perform gynecological brachytherapy (21).

In order to combat this problem, the present prospective study analyzed the feasibility and safety of radiosensitization treatment using hydrogen peroxide for patients with cervical cancer who cannot undergo brachytherapy. In order to be considered as a suitable option for patients who are unsuitable for brachytherapy, radiosensitization treatment must be proved to be non-inferior compared with standard treatment, including brachytherapy. Yang *et al* (22) analysed the Surveillence, Epidemiology, and End Results database to compare the prognostic impact of several treatment modalities, including RT with or without brachytherapy, for cervical cancer. They showed that external-beam RT alone was, in most cases, less effective than combined external-beam RT and brachytherapy.

Quinn *et al* (23) reported the results of a multi-institutional international retrospective survival analysis of 15,081 patients. Among them, the 1,655 patients who received RT with brachytherapy had 1- and 2-year survival rates as follows: Stage IB1, 95.8 and 85.2; IIA, 94.0 and 83.7; IIB, 92.2 and 81.5 and IVA, 74.0 and 48.6%. Corresponding rates in the present study were 100 and 100 (4/4) for stage IB1 and IIA, 83 and 83 (5/6) for IIB, 100 and 100 (2/2) for IIIB and 80 and 80% (4/5) for IVA. Since the patient population was small, the reliability of this comparison is limited, but it is encouraging that the present results were not notably worse than standard treatment. Therefore, this method may be an option for patients who are unsuitable for or unable to undergo brachytherapy.

Retrospective reports regarding patients with cervical cancer who did not undergo brachytherapy and received only external-beam RT are summarized in Table V (24-29). The one- and two-year OS was 74-100 and 43-64%, which was comparable to the present study. Regarding late toxicity, studies including total dose >70 Gy (24,25) or accelerated hyperfractionation (26), the number of patients with Grade 2 or worse late toxicity was 10-23.7%. On the other hand, studies with conventional fractionation where the dose did not exceed 70 Gy, late toxicity was 0.7-9.1%. In the present study there was no late toxicity; the total radiation dose used was 45 Gy. In the aforementioned studies, no patients received a total dose <55 Gy.

Table IV. Adverse events assessed according to Common Terminology Criteria for Adverse Events (version 4.0).

	Grade				
Adverse event	0	1	2	3	4
Mucositis	8 (47.1%)	8 (47.1%)	1 (5.9%)	0	0
Diarrhea	2 (11.8%)	10 (58.8%)	4 (23.5%)	1 (5.9%)	0
Cystitis	0	0	0	0	0
Neutropenia	7 (41.2%)	2 (11.8%)	4 (23.5%)	4 (23.5%)	0
Anemia	1 (5.9%)	8 (47.1%)	4 (23.5%)	3 (17.7%)	0
Thrombocytopenia	9 (52.9%)	5 (29.4%)	2 (11.8%)	1 (5.9%)	0
Nausea	10 (58.8%)	6 (35.3%)	1 (5.9%)	0	0
Late	0	0	0	0	0

All observed adverse events were acute; no late adverse events were observed.

Table V. Retrospective reports of patients with cervical cancer who were unable to recieve brachytherapy and received external-beam radiotherapy alone.

Author, year	Number of patients	Stage	Treatment	PFS	OS	Late toxicity
The present study	17[a]	IB-IVA[a]	Pelvis, 45 Gy/25 fx	1 year, 69.0%; 2 year, 55.2%	1 year, 81.6%; 2 year, 68.0%	GI, 0% (any); GU, 0% (any)
Karlsson *et al*, 2017 (24)	86	I-IV	Pelvis, 46-68 Gy/23-34 fx; Tumor boost, 6-26 Gy/3-13 fx	NR	1 year, 70.0%[b]; 2 year, 50.0%[b]	GI, 23.7% (grade 2-4); GU, 10.5% (grade 2-4)
Barraclough *et al*, 2008 (25)	44	IB-IVA	Pelvis, 40-45 Gy/25 fx; Tumor boost, 15-25 Gy/8-10 fx	NR	1 year, 81.4%; 2 year, 64.0%	GI, 9.1% (grade 2); GU, 2.3% (grade 3)
Matsuura *et al,* 2012 (26)	16	IIB-IVA	Pelvis, 45 Gy/25 fx; Tumor boost (AHF), 9-15 Gy/6-10 fx	NR	3 year, 43.8%	GI, 12.5% (grade 2-4); GU, 12.5% (grade 2)
Ito *et al*, 2019 (27)	37	IB-IVA	Pelvis, 45-50 Gy/25 fx; Tumor boost, 6-10 Gy/3-5 fx	1 year, 45.0%; 2 year, 29.0%	1 year, 74.0%; 2 year, 43.0%	GU, 2.7% (grade 4); GU, 2.7% (grade 4)
Park *et al,* 2010 (28)	10	IIA-IIIB	Pelvis, 40-50 Gy/20-25 fx; Tumor boost, 25-30 Gy/6-12 fx	NR	1 year, 100%	GI, 10.0% (grade 2); Subcutaneous abscess, 10.0%
Saibishkumar *et al,* 2006 (29)	146	I -IVA	Pelvis, 46 Gy/23 fx; Tumor boost, 14-20 Gy/7-10 fx	5 year, 11.6%	5 year, 15.1%	GI, 0.7% (grade 3); GU, 0.7% (grade 3)

[a]Excluding patient with tumor *in situ*. [b]Cancer-specific survival. PFS, progression-free survival; OS, overall survial; Gy, gray; fx, fraction; GI, gastrointestinal; GU, genitourinary; AHF, accelerated hyperfractionation; NR, not reported.

Univariate and multivariate by Ito *et al* (27) showed that maximum primary tumor diameter >5 cm is associated with significantly worse PFS.

Karlsson *et al* (24) compared the outcomes of patients underoing RT with brachytherapy with those of patients receiving external-beam RT boost (EBRB) instead of brachytherapy; the brachytherapy group fared better overall. The cancer-specific survival at one- and two-year was ~95 and 85% for the brachytherapy group and 70 and 50% for the EBRB group. However, in patients with International Federation of

Gynecology and Obstetrics stages III-IV, there was no significant difference in cancer-specific survival rate between the two groups.

Yoshida *et al* (30) reported that, for patients with tumors >5 cm, satistfactory outcomes were achieved by high quality image-guided adaptive brachytherapy with interstitial brachytherapy. Similar results was observed in the present study, where the one- and two- year local control rates were 100 (17/17) and 93% (14/15), respectively and the one- and two- year CR rates for all stages combined were 82 (14/17) and 59% (10/17), respectively. In the present study all five patients with local recurrence had a tumor diameter >5 cm, whereas among the six patients with stage IIB cancer, only two achieved CR. By contrast, the two patients with stage IIA cancer both experienced CR without recurrence for more than four years. It may be that, similar to brachytherapy, tumor size is associated with the treatment outcome. Therefore, patients with smaller cervical tumors that do not develop toward the pelvic wall may benefit from radiosensitization treatment. However, patients who are not candidates for traditional brachytherapy but have larger tumors or those with advanced stage lesions may fare better with EBRB (24).

The present study is not without limitation. First, as aforementioned, the patient population was small and the observation time was relatively short. Furthermore, the radiation dose was relatively low in consideration of potential salvage surgery in case of residual tumor following RT. One of the present patients underwent salvage surgery.

Hong *et al* (31) reported that salvage surgery performed for cervical cancer following definitive RT with doses up to 54 Gy does not cause severe complications and achieves long-term survival. Therefore, increasing the dose or delivering additional EBRB to the uterus and cervix may improve results. Additionally, Ogawa *et al* (11) reported the safety of hydrogen peroxide solution-soaked gauze bolus on the skin during each RT session; however, in the present study, patients received KORTUC to the vaginal mucosa during only 2 of the 5 weekly RT sessions. Based on our safety results (Table IV), more frequent use of a vaginally inserted hydrogen peroxide solution-soaked gauze may improve outcomes.

In the present study, radiosensitization treatment using hydrogen peroxide appeared to be safe and feasible in patients with cervical cancer. This treatment could be a promising option for patients with small tumors that do not extend toward the pelvic wall who cannot undergo brachytherapy.

Future research, including clinical trials, is warranted to determine the efficacy of this treatment. For much of the prior experience is with injected KORTUC, theoretically, injection of KORTUC dirctly into the tumor may extend its benefits into deep tumor tissues. Future studies should investigate the efficacy of injection of KORTUC in patients with cervical cancer during RT.

Radiosensitization with gauze insertion before each radiation dose may improve treatment outcome. A synergistic effect may be achieved by combining KORTUC and brachytherapy. Moreover, increasing the radiation dose or delivering additional EBRB to the uterus and cervix might improve results. KORTUC is a promising method and future research should investigate how to maximize patient benefit.

Acknowledgements

The authors would like to thank Dr Robert Kneller (University of Tokyo, Japan) for helpful comments.

Funding

No funding was received.

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

AIS, TM, TI, TO, TU and KY obtained the data. RH and AIS conceptualized and designed the study, analyzed and interpreted data and drafted the manuscript. AIS and RH confirm the authenticity of all the raw data. KS was involved in the concept and design of the study. All authors revised the manuscript critically for important intellectual content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of Juntendo University Urayasu Hospital (approval no. 2014-008). Informed consent was obtained from all patients.

Patient consent for publication

Written informed consent for publication was obtained from all patients enrolled in the present study.

Competing interests

The authors declare that they have no competing interests.

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