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Modulated electrohyperthermia in locally advanced cervical cancer

Results of an observational study of 95 patients

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Abstract

Most federation of gynecology and obstetrics stage II or higher locally advanced cervical cancer (LACC) patients are treated with concurrent chemoradiotherapy (CCRT); however, recurrence is high, and the prognosis is poor. In this observational retrospective study, data from LACC patients treated with CCRT alone or combined with modulated electrohyperthermia (mEHT) were collected from 2011 to 2018. Ninety-five LACC patients, including 53 (%) treated with CCRT alone and 42 (%) treated with CCRT + mEHT, were enrolled. The complete remission rate significantly increased with CCRT + mEHT compared with CCRT alone among LACC cases with lymph node metastasis (45% vs 71%, *P* = *.0377*). Additionally, at the last follow-up point, the no-evidence-of-disease rate significantly improved with CCRT + mEHT compared with CCRT (58% vs 82%, *P* = *.0315*). Disease-free survival increased in the CCRT + mEHT group with lymph node metastasis (*P* = *.04*). The addition of mEHT to CCRT led to a better therapeutic response in LACC with regional lymph node metastasis without severe complications.

Abbreviations: AEs = adverse events, CCRT = concurrent chemoradiotherapy, CR = complete remission, DFS = disease-free survival, HIF-1a = hypoxia-inducible factor-1a, LACC = locally advanced cervical cancer, mEHT = modulated electrohyperthermia, NED = no-evidence-of-disease, OS = overall survival, RF = radio frequency, VEGF = vascular endothelial growth factor.

1. Introduction

Cervical cancer is the fourth most common cancer in women, with 5,70,000 patients being diagnosed and 3,11,000 deaths occurring in 2018 worldwide.[1] In particular, some developing countries, including Africa, have the highest cancer incidence and mortality rates among women.[1,2] Treatment of cervical cancer includes surgery, radiotherapy, and chemotherapy. For locally advanced cervical cancer (LACC), cisplatin-based concurrent chemoradiation therapy (CCRT) is commonly accepted as the primary treatment, and this treatment has been proven to lead to better outcomes than radiation alone.[3–6] Surgical treatment for LACC usually requires adjuvant radiation and has a similar survival rate but is accompanied by various complications.[7] Although the incidence of cervical cancer is decreasing due to the development of screening tests and vaccines for human papillomavirus (HPV), patients diagnosed with LACC still have a high recurrence rate and a poor prognosis even if they are treated with the standard therapy, namely, CCRT.[8]

Modulated electrohyperthermia (mEHT), which was used in the present study, is a type of hyperthermia used in oncological treatments that avoids the drawbacks of conventional electromagnetic heating.[9,10] This treatment device is designed to selectively heat malignant tumors and tumor cells by modularly delivering 13.56 MHz radio frequency (RF).[11–14] This method works by heating malignant cells, selectively and effectively acting on the cell membrane,[15] and inducing apoptotic cell death.[9] This advanced treatment produces damage-associated cellular patterns and promotes immunogenic cell death accompanied by the release of damage-associated molecular signal patterns, such as ATP, HMGB1 and hsp70, which have the cytokine-like effects of attracting immune cells.[16,17] The heat-induced increase in the tumor response to radiotherapy is due, at least in part, to an increase in the oxygen supply via increased blood circulation in tumors. The enhanced response of tumors to chemotherapy may be due to various factors. First, mild heating increases the delivery of chemotherapeutic drugs to the tumors by increasing blood flow to and within the tumor. Second, mild heating increases the cellular uptake of drugs by increasing cell membrane permeability. Third, heating facilitates the reaction rate of drugs, which potentiates their cytotoxicity.[11,16]

This method uses a modulated RF for energy delivery and achieves selective thermal action in nonhomogeneous tissue.[18]

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It is also notably gentle, and its use on brain malignancies has been successful,[19–21] even at increased doses for advanced cases.[12]

In the present study, we analyzed whether there was a better treatment by analyzing the treatment results and recurrence rates of the 2 treatment groups that underwent CCRT alone or CCRT + mEHT for locally advanced cervical cancer.

2. Methods

2.1. Patient selection

All patients with LACC who were treated from January 2011 to December 2018 with CCRT and mEHT at Jeonbuk National University Hospital were included, and patients who underwent follow-up for more than 3 years were analyzed. Data were collected retrospectively, and patients were selected according to the following inclusion criteria: > 18 years of age, stage II, III, or IV cervical cancer, treatment with CCRT alone or in combination with mEHT, and signed informed consent.

Routine pretreatment work-up consisted of gynecological examination, CT, and MRI scan. Lymph node enlargement on CT or MRI scan is considered clinically positive. A total of 95 patients were enrolled. Fifty-three (%) patients were treated with CCRT alone, and 42 (%) patients were treated with CCRT and mEHT. The patient group was classified using the cancer stage process presented in the 2008 federation of gynecology and obstetrics guideline (Table 1).

2.2. CCRT

Most patients underwent chemotherapy with cisplatin alone, and a few were treated with cisplatin + 5-FU, cisplatin + etoposide and oral 5-FU.

Chemotherapy was started at the same time as radiation therapy, and in the hyperthermia combination group, treatment was carried out on the same day as chemoradiation therapy. Chemotherapy was performed more than 5 times in most patients.

Chemotherapy-associated adverse events (AEs) were pancytopenia, nausea, vomiting, anorexia and gastric discomfort. AEs were determined by investigator inquiry and by spontaneous patient reports. The AEs were recorded with regard to the symptoms, signs, duration and severity (mild, moderate, and severe). Clinical safety parameters, including blood glucose levels, vital signs, 12-lead ECG results and clinical laboratory tests, were observed during the regular chemotherapy cycles. For radiation therapy, after all patients received external radiation therapy with a mean total radiation dose of 54 Gy, an additional boost was administered according to the patient's condition, brachytherapy (6 times, 24 Gy) or external radiation

Table 1

Characteristics of patients with cervical cancer who had previously undergone chemoradiotherapy, who were subsequently subjected to CCRT alone or who received CCRT combined with mEHT.

Parameter	CCRT alone (n = 53, 56%)	CCRT + mEHT (n = 42, 44%)	*P* value
Age, yr	58.7 (28–81)	51.8 (26–78)	.25
mean			
FIGO stage	2 (4%)	1 (2%)	
IIA	44 (83%)	32 (77%)	
IIB	2 (4%)	1 (2%)	
IIIA	5 (9%)	8 (19%)	
IIIB			
Pathology			
squamous cell	45 (85%)	37 (88%)	.157
carcinoma	6 (11%)	4 (10%)	
adenocarcinoma	2 (4%)	1 (2%)	
other			
Pelvic lymph	31 (58%)	34 (81%)	
node status	22 (42%)	8 (19%)	
positive			
negative			

CCRT = concurrent chemoradiotherapy, FIGO = federation of gynecology and obstetrics, mEHT = modulated electrohyperthermia.

Table 2

Chemotherapy treatment characteristics of CCRT alone and CCRT combined with mEHT.

	CCRT alone (n = 53)	CCRT + mEHT (n = 42)
Chemotherapy regimen		
Cisplatin	52 (98%)	35 (84%)
6 cycles	45	31
5 cycles	3	2
4 cycles	4	1
3 cycles	0	1
Cisplatin + 5-FU	0	6 (14%)
(3–7 cycles)		
Cisplatin + etoposide	0	1 (8 cycles, 2%)
5-FU	1 (oral) (2%)	0

CCRT = concurrent chemoradiotherapy, mEHT = modulated electrohyperthermia.

Table 3

Clinical response of CCRT alone and CCRT-combined with mEHT following completion of treatment.

	CCRT alone (n = 53)	CCRT + mEHT (n = 42)	*p* value
response after 1st Tx			
CR	28 (53%)	30 (71%)	.0649
Non-CR	25 (47%)	12 (29%)	
response after last F/U			
NED	36 (68%)	35 (83%)	.0861
Non-NED	17 (32%)	7 (17%)	

CCRT = concurrent chemoradiotherapy, CR = complete remission, mEHT = modulated electrohyperthermia, NED = no-evidence-of-disease.

therapy (mean 7 times, 12.4 Gy). Side effects related to radiation therapy included abdominal discomfort and frequent urination, and no serious life-threatening side effects occurred (Table 2).

2.3. mEHT protocol and device

Modulated electrohyperthermia treatment was applied using an EHY2000 clinical heating device (Oncotherm GmbH, Troisdorf, Germany) set at a 13.56 MHz carrier frequency, and the amplitude was modulated according to a time fractal pattern. Modulated electrohyperthermia was performed for 60 minutes. The patients were placed in the supine position on a water mattress electrode. A circular upper electrode (30 cm diameter) was coupled over the pelvic area. Prior to mEHT, all patients underwent a 2-dimensional simulation. The treatment field encompassed the mass with a 3-cm margin in the X, Y directions. Modulated electrohyperthermia was performed 3 times per week beginning at the initiation of CCRT, and patients underwent 24 to 36 sessions (mean 28.6 times).

The power output was 80 W for the first 10 minutes, 120 W for the next 10 minutes, and 150 W for the remaining treatment time. Self-calibration of the device was performed prior to each treatment. The body temperature, blood pressure and pulse rate of each patient were measured prior to, during and following treatment. Body temperature was measured using an infrared ear thermometer (Infrared Thermometer IRT 4020; Braun GmbH, Kronberg, Germany), and the temperature of the abdominal skin surface below the circular upper electrode probe was measured using a non-contact infrared thermometer transmitter (Thermo Checker DT-060; Easytem Co., Ltd., Siheung, Korea). AEs associated with hyperthermia and chemotherapy were monitored throughout the present study. Hyperthermia-associated AEs were warm sensation, skin burn and gastric discomfort.

2.4. Statistical analysis

The end points of the present study were tumor response with complete remission (CR) or partial remission, stable disease or progressive disease, overall survival, final follow-up status and toxicity. Student's t-test was used for treatment response analysis.

The time to an event variable was estimated using Kaplan–Meier analysis. The statistical analysis was performed using SAS software (version 9.3; SAS Institute, Inc., Cary, NC). A P value < .05 was considered statistically significant.

2.5. Ethics statement

The present study was approved by the Institutional Review Board of Jeonbuk National University Hospital (Jeonju, Republic of Korea, JBNU IRB NO. 2018-06-009-002) and was conducted according to the Declaration of Helsinki regarding biomedical research involving human subjects and the Guidelines for Good Clinical Practice and written the informed consent was obtained from all patients legal guardian.

3. Results

3.1. Patient characteristics

The study included 95 consecutive patients, 53 (56%) of whom received CCRT alone and 42 (44%) of whom received CCRT and mEHT. The patient characteristics are summarized in Table 1.

The mean age, cancer stage, pathology type, and lymph node metastasis were not significantly different between the 2 groups. The mean ages were 58.7 and 51.8 years, and all patients were diagnosed with stage IIA-IIIB disease. Most patients were diagnosed with squamous cell carcinoma (P = .157) based on cervical biopsy using the vaginal approach. The frequency of lymph node metastasis was higher in the CCRT + mEHT group, but the difference was not significant.

3.2. Outcome

Most patients were treated with cisplatin-based CCRT for 6 cycles. A small number of patients were treated with other chemotherapies, but the number was not significant (Table 2).

The CR rates of the 2 groups were 53% and 71%, respectively (P = .0649), and the no-evidence-of-disease (NED) rates at the last follow-up were 68% in the CCRT-alone group and 83% in the CCRT + mEHT group (P = .0861); however, the differences were not significant (Table 3). There was also no significant difference in disease-free survival (DFS) or overall survival (OS) (P = .166 and 0.079, respectively) (Fig. 1).

However, in the separate analysis of patients with pelvic lymph node metastasis, significant variation in the results was observed. More patients showed CR with CCRT + mEHT treatment (45% vs 71%, P = .0377) and more NED (58% vs 82%, P = .0315) (Table 4). There was no difference in OS (P = .10), but a significant difference in DFS was observed (P = .04) (Fig. 2).

3.3. AEs associated with hyperthermia and chemotherapy

Hyperthermia-associated AEs were warm sensation, skin burn and gastric discomfort. The 18 patients (42.8%) complained of warm sensation in treatment area, 4 patients (9.5%) complained of first-degree burns on treatment areas, and 6 patients (14.2%) complained of mild gastric discomfort. All patients' AEs disappeared immediately after treatment without any additional treatment.

4. Discussion

The basic treatment principle of cervical cancer is to remove the primary cancer lesion and remove the potential spread site. The

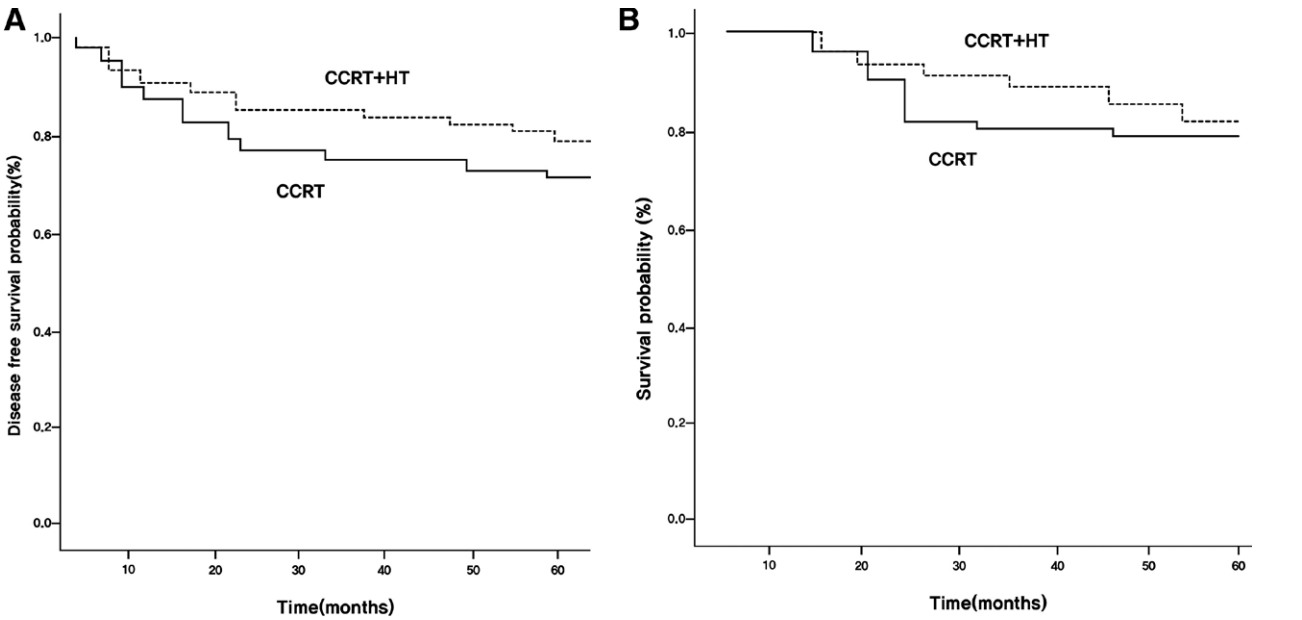

Figure 1. (A,B): Disease-free survival and overall survival of patients treated with CCRT alone compared with those treated with CCRT combined with mEHT. CCRT combined with mEHT did not significantly increase the disease-free survival rate or overall survival rate (P = .166 for DFS, P = .079 for OS). CCRT = concurrent chemoradiotherapy, DFS = disease-free survival, mEHT = modulated electrohyperthermia, OS = overall survival.

Table 4

Clinical response of CCRT alone and CCRT-combined with mEHT following completion of treatment in patients with pelvic lymph node metastasis.

LN metastasis	CCRT alone (n = 31)	CCRT + mEHT (n = 34)	*p* value
Response after	14 (45%)	24 (71%)	.0377
1st Tx	17 (56%)	10 (29%)	
CR			
Non-CR			
Response after	18 (58%)	28 (82%)	.0315
last F/U	13 (42%)	6 (18%)	
NED			
Non-NED			

CCRT = concurrent chemoradiotherapy, CR = complete remission, mEHT = modulated electrohyperthermia, NED = no-evidence-of-disease.

primary treatment is to perform surgery or radiotherapy after setting the clinical stage. Surgical treatment can be performed for cancers up to stage IIA that are limited to the cervix and upper vagina. Radiation therapy can be used to treat all stages and has similar treatment results to those of surgical treatment.

Several studies have shown that CCRT improves the therapeutic outcomes of LACC patients, whose therapeutic outcomes would otherwise be poor with radiation therapy alone.[3,4,22] However, despite treatment with CCRT, patients with LACC still have locoregional recurrence and distant metastasis at a frequency of 27% to 35% and a high mortality rate and poor prognosis in cases of recurrence.[23] Hyperthermia can directly kill cancer cells through heat and increase blood flow to the warmed area and tumor oxygenation. In addition, the effect of chemotherapy can be improved by increasing the intracellular drug concentration through an increase in permeability with membrane damage, an increase in drug uptake, and a change in pH. By increasing the possibility of cell damage and preventing damage recovery, the effect of radiation can be increased.[9] Conventional hyperthermia, at > 43°C or higher, has several limitations. As normal tissue and malignant tissue receive homogeneous heat, the focus of temperature does not match the focus of energy; therefore, temperature does not simply correlate with energy to damage the cancer cell. The energy transfer to the tumor is indirect and difficult to measure. In addition, this homogeneous heating of normal tissues surrounding tumors can increase blood flow and the supply of nutrients to the tumor and can lead to an increase in invasion, dissemination, and metastasis.[16] Oncothermia is a modular electrohyperthermia based on energy dose control instead of a single parameter of temperature, and this method accurately selects only tumor cells and heats them to transfer a definite energy dose to more effectively lead to apoptotic cell death without unwanted physiologic consequences.[11] Using anesthetized living pigs, Balogh et al[19] reported that 13.56 MHz-modulated RF can increase the temperature by 3 to 5°C in deep tissue. Kim et al[24] reported that mild temperature hyperthermia suppresses hypoxia-inducible factor-1a (HIF-1a) and vascular endothelial growth factor (VEGF), which are upregulated under hypoxic conditions. When only 15 Gy (60 Co) irradiation was performed in FSa fibrosarcoma allograte in C3H mice, blood perfusion was decreased, hypoxia increased, and HIF-1a and VEGF were upregulated, but when mild temperature hyperthermia treatment was performed after irradiation, blood perfusion and tumor oxygenation were increased, and HIF-1a and VEGF were suppressed.[25] Lee et al[20] reported increased blood

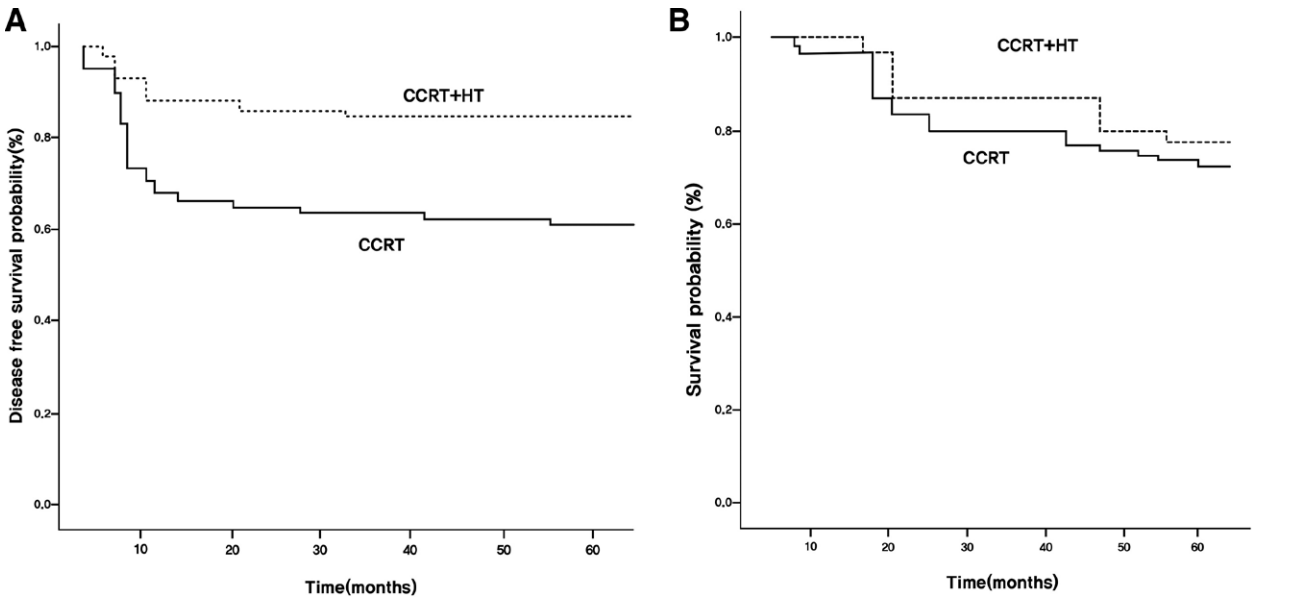

Figure 2. (A,B): Disease-free survival and overall survival of patients with lymph node metastasis compared to patients without lymph node metastasis treated with CCRT alone and CCRT combined with mEHT. DFS, but not OS, was significantly different between the two groups (P = .04 for DFS, P = .104 for OS). CCRT = concurrent chemoradiotherapy, DFS = disease-free survival, mEHT = modulated electrohyperthermia, OS = overall survival.

perfusion to the tumor and increased peritumor temperature from 36.7 ± 0.2°C to 38.5 ± 0.8°C through mEHT in patients with cervical cancer. Vancsik et al[17] reported that mEHT promotes doxorubicin uptake and potentiates doxorubicin-induced cytotoxic effects in the case of a combination of doxorubicin and mEHT in C26 mouse colorectal adenocarcinoma culture. Recently, several studies on the clinical effectiveness and stability of the combination of conventional therapy and mEHT have been reported. Fiorentini et al[21] reported that when chemotherapy, radiotherapy, and mEHT were combined in patients with stage III-IV pancreatic cancer, the tumor response was improved, and the median overall survival increased from 10.9 months to 18.0 months. A study comparing the effects of supportive care and mEHT in relapsed malignant astrocytoma and glioblastoma reported that the 5-year survival rate of astrocytoma was increased from 25% to 83% in the mEHT group.[20] Gadaleta-Caldarola et al[26] reported that sorafenib plus mEHT combination therapy in advanced hepatocellular carcinoma was feasible and well tolerated without major complications. Grade 4 treatment-related toxicities were not observed, and grade 3 toxicities were related to only sorafenib, not mEHT.[7] In our study, we compared the treatment response of the CCRT treatment group and CCRT + mEHT treatment group for LACC. There was no difference in response rate (CR and NED) between the 2 groups, and DFS and OS also showed no significant difference. However, the CR rate was significantly increased in the CCRT + mEHT group compared to the CCRT alone group in the case of locally advanced cancer (stage IIIC) in women with lymph node metastasis (P = .0377). Additionally, at the last F/U point, the NED rate also showed a significant improvement compared to the CCRT alone group (P = .0315). DFS also improved in the CCRT + mEHT group with lymph node metastasis (P = .04). In 1 study about recurrent cervical cancer in women who were previously irradiated with chemotherapy combined with mEHT compared with chemotherapy alone, the authors concluded that hyperthermia may be slightly more effective for the treatment of abdominal lymph node metastasis.[27] In the 2018 International Federation of Gynecology and Obstetrics staging system for uterine cervical cancer, pelvic or para-aortic lymph node metastasis was classified as stage IIIC.[28] However, there is no change in therapeutic modality, namely, CCRT. In our study, mEHT combined with CCRT led to a better therapeutic response in patients with LACC with regional lymph node metastasis without severe complications. However, there is a limitation in that this study is a single-center study, has a small number of participants, and cannot explain the pathogenesis, namely, why better results were found in patients with lymph node metastasis. In conclusion, to obtain better treatment results, further discussion or research regarding combined hyperthermia therapy should be conducted. Additional cell-level studies and laboratory studies are also needed to determine why mEHT is more effective in lymph nodes, and large-scale prospective studies are needed in patients with federation of gynecology and obstetrics stage IIIc disease.

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