

# Treatment outcome analysis of chemotherapy combined with modulated electro-hyperthermia compared with chemotherapy alone for recurrent cervical cancer, following irradiation

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**Abstract.** The survival of patients with recurrent cervical cancer following irradiation remains poor. Chemotherapy combined with hyperthermia has been demonstrated to improve the response rate. The present study was performed to evaluate the effect of modulated electro-hyperthermia combined with conventional chemotherapy compared with chemotherapy alone on recurrent cervical cancer previously treated with irradiation. A total of 20 patients were treated with chemotherapy alone, and 18 were treated with chemotherapy combined with modulated electro-hyperthermia. A single patient was treated with chemo-radiotherapy as primary treatment and then relapsed; the tumor was inoperable and radio-refractory upon recurrence. Local metastases, including metastasis of the para-aortic lymph nodes and adjacent pelvic lymph nodes were included, but distant metastases were excluded. Modulated electro-hyperthermia was performed three times per week beginning at chemotherapy initiation, and patients underwent a total of 36 sessions. The overall response (complete remission + partial remission + stable disease/progressive disease) to treatment was significantly greater in the group of patients who underwent chemotherapy combined with modulated electro-hyperthermia ( $P=0.0461$ ), and at the evaluation conducted at the last follow-up visit, the response rate was significantly higher ( $P=0.0218$ ). Additionally,

severe complications were not reported. In the present study, of patients with recurrent cervical cancer previously treated with irradiation, the overall response rate for patients treated with chemotherapy combined with modulated electro-hyperthermia was significantly greater than that for those treated with chemotherapy alone.

## Introduction

Carcinoma of the uterine cervix is the fourth most common female malignancy globally, following breast, colorectal and lung cancers (1). In developed countries, including the USA, ~12,900 women are diagnosed with cervical cancer and ~4,100 mortalities per year are attributed to this disease (2). The 5-year overall survival rate is 68% for all stages of cervical cancer; however, the survival rate is 91% when the disease is diagnosed in an early phase. Patients with metastases in regional lymph nodes only have a 57% 5-year survival rate, and those with distant metastases only have a 16% 5-year survival rate. The overall 5-year survival rate is relatively high in Korea (80-81.2% over the last 15-year period) (3). Increased cancer screening and updated treatment strategies are key factors that have produced improved results (4). Specifically, the survival of women with recurrent cervical cancer or para-aortic lymph node (PAN) metastasis remains poor. More effective treatment methods and regimens are therefore needed. Cisplatin is an effective single therapeutic regimen for first-line therapy, but single-agent regimens for recurrent cervical cancer have a poor response rate (only 13%) (5). The recurrence rate is lower for patients with a pelvic recurrence within previously irradiated areas than for those with extra-pelvic sites of disease. In addition, the responsiveness of pelvic recurrences is partial at best and has a brief (median 4-6 months) duration (6). To enhance the therapeutic response, chemotherapy was combined with hyperthermia (cisplatin + hyperthermia for previously radiated cases), which has been demonstrated to be feasible (7) when used in tri-modal applications for the cervix (8-11). By using local hyperthermia and systemic administration of chemotherapy, it

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is possible to achieve maximum synergism without increasing the systemic side effects, which primarily affect the bone marrow and kidneys (12). Modulated electro-hyperthermia, which was used in the present study, is a type of hyperthermia used in oncological treatments that avoids the drawbacks of conventional electromagnetic heating (13,14). This treatment device is designed to selectively heat malignant tumors and tumor cells by modularly delivering 13.56 MHz RF (15-18). This method works by heating the malignant cells, selectively and effectively acting on the cell membrane (19), and inducing apoptotic cell death (20). This advanced treatment produces damage-associated cellular patterns and promotes immunogenic cell death (21). 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 three factors. First, mild heating increases the delivery of chemotherapy 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 (21,22).

This method uses modulated radiofrequency for energy delivery and achieves selective thermal action in non-homogeneous tissue (23). It is also notably gentle, and its use on brain malignancies has been successful (24-26), even at increased doses for advanced cases (16). Modulated electro-hyperthermia does not cause pain and has fewer side effects, which results in improved patient satisfaction and quality of life (18). Patients treated with modulate electro-hyperthermia have reported pain relief (23) and, as a result, a decreased dose of analgesic is required (22). The aim of the present study was to evaluate the effect of modulated electro-hyperthermia combined with conventional chemotherapy compared with chemotherapy alone on recurrent cervical cancer previously treated with irradiation, by analyzing the outcomes of patients subjected to each treatment. The objectives of the present study were to determine the local control, treatment outcome and side effects.

## Materials and methods

**Ethics statement.** The present study was approved by the Institutional Review Board of Chonbuk National University Hospital (Jeonju, Republic of Korea) and was conducted according to the Declaration of Helsinki regarding biomedical research involving human subjects and the Guidelines for Good Clinical Practice. Written, informed consent was obtained from all patients.

**Patients.** A total of 20 subjects were included in the chemotherapy only group, and 18 subjects were included in the chemotherapy combined with modulated electro-hyperthermia group and all patients underwent treatment at the Chonbuk National University Hospital (Table I). Patients were included in the present study if they had histologically confirmed cervical cancer (histological diagnosis of squamous cell carcinoma or adenocarcinoma) and if complete remission (CR) was achieved following first-line treatment. In addition, a patient who experienced recurrence following surgery and chemo-radiotherapy

was included in the present study. A patient who received chemo-radiotherapy as primary treatment suffered a relapse; the tumor was inoperable and radio-refractory following recurrence. Local metastases were included, for example metastasis of the PANs or the adjacent pelvic lymph nodes (PLNs), but distant metastases were excluded. The selected patients were required to have an ECOG status of  $\leq 3$ . Patients underwent 36 modulated electro-hyperthermia sessions and at least 6 months of follow-up. Patients in the chemotherapy only group had the following indications: 1, recurrence in a PAN alone or in a PLN and/or the bed of the cervix; 2, no distant metastasis (excluding PANs); 3, radiotherapy was not possible due to recurrence in a previous radiotherapy field; and 4, at least 6 months of follow-up.

Patients in the chemotherapy combined with modulated electro-hyperthermia group had the following indications: i) Recurrence in a PAN or PLN and the bed of the cervix (specifically, in the 30 cm probe treatment area); ii) no distant metastasis (excluding PANs); iii) 36 sessions of hyperthermia therapy (3 sessions per week); iv) radiotherapy was not possible due to recurrence in a previous radiotherapy field; and v) at least 6 months of follow-up.

**Chemotherapy.** All patients received platinum-based chemotherapy for recurrence according to local hospital policy. The treatment characteristics are summarized in Table II. Depending on local hospital policy, the goal of combined chemotherapy with modulated electro-hyperthermia was to administer 36 sessions of modulated electro-hyperthermia during chemotherapy. All patients were evaluated for toxicity each week.

**Modulated electro-hyperthermia.** Modulated electro-hyperthermia 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 electro-hyperthermia was performed for 60 min. The patients were placed in a supine position on a water mattress electrode. A circular upper electrode (30 cm in diameter) was coupled over the recurrent cervical mass or PAN mass. Prior to modulated-electro hyperthermia, all patients underwent a two-dimensional simulation. The treatment field encompassed the mass with a 3 cm margin in the X, Y, and Z directions. Modulated electro-hyperthermia was performed three times each week beginning at the initiation of chemotherapy, and patients underwent a total of 36 sessions.

The power output was 80 W for the first 10 min, 120 W for the next 10 min and 150 W for the remaining treatment time. Self-calibration of the device was performed prior to each treatment (11). 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). Adverse events (AEs) of the associated-hyperthermia and chemotherapy were monitored

Table I. Characteristics of patients with recurrent cervical cancer who had previously undergone chemo-radiotherapy, who were subsequently subjected to chemotherapy alone or chemotherapy combined with modulated electro-hyperthermia.

Parameter	Chemotherapy alone (n=20)	Chemotherapy and modulated electro-hyperthermia (n=18)
Age, years		
Range	36-71	36-71
Mean	53	50.8
FIGO stage		
Ib	2	3
IIa	3	3
IIb	3	3
IIIa	5	2
IIIb	4	4
IVa	3	3
Pathology		
Squamous cell carcinoma	15	15
Adenocarcinoma	5	3
Recurrent lesions		
Cervix bed alone	4	6
PAN alone	4	4
Iliac LN alone	4	5
Iliac LN+cervix bed	8	3

PAN, para-aortic lymph node; LN, lymph node.

Table II. Treatment characteristics of the chemotherapy alone and chemotherapy combined with modulated electro-hyperthermia groups.

Group	TP (cycle)	TC (cycle)	FP (cycle)	Cisplatin (cycle)
Chemotherapy alone (n=20)	8 (5-7)	6 (6-9)	6 (4-6)	0
Chemotherapy and modulated electro-hyperthermia (n=18)	6 (5-6)	4 (6)	6 (4-6)	2 (5-6)

TP, paclitaxel+cisplatin; TC, paclitaxel+carboplatin; FP, cisplatin+5-fluorouracil.

Table III. Clinical response of the chemotherapy-alone and the chemotherapy-combined with modulated electro-hyperthermia groups following completion of treatment.

Group	Complete remission	Partial response	Stable disease	Progressive disease	P-value
Chemotherapy alone (n=20)	4	3	1	12	0.0461
Chemotherapy and modulated electro-hyperthermia (n=18)	9	2	2	5	

throughout the present study. Hyperthermia-associated adverse events were hot sensation, skin burn and gastric discomfort. Chemotherapy-associated adverse events 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 (3-4 weeks intervals).

*Statistics.* The end points of the present study were tumor response [CR, partial remission (PR), stable disease (SD) and

Table IV. Analysis of the last follow-up treatment response to chemotherapy alone or chemotherapy combined with modulated electro-hyperthermia.

Group	Complete remission	Partial response	Stable disease	Progressive disease	P-value
Chemotherapy alone (n=20)	3	3	1	13	0.0218
Chemotherapy and modulated electro-hyperthermia (n=18)	9	2	2	5	

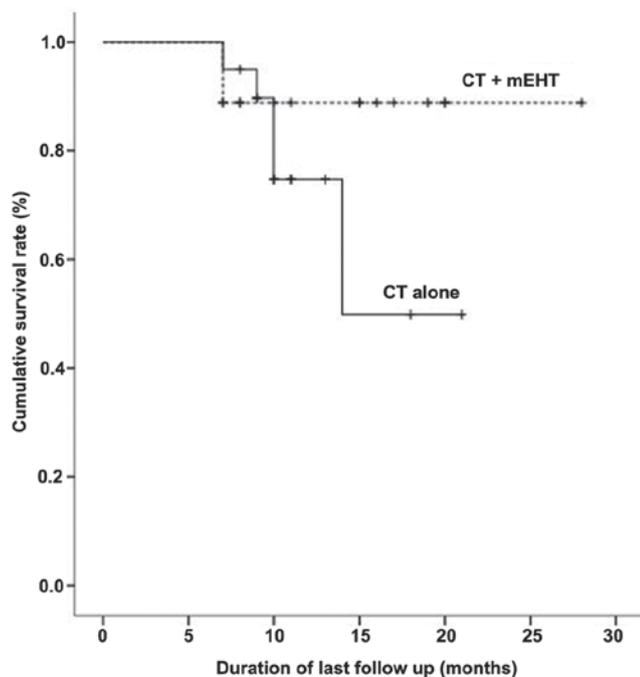


Figure 1. Overall survival of the patients treated with chemotherapy alone compared with those subjected to CT combined with mEHT groups. CT combined with mEHT did not significantly increase the overall survival rate ( $P=0.235$ ). CT, chemotherapy; mEHT, modulated electro-hyperthermia.

progressive disease (PD)], 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, USA).  $P < 0.05$  was considered to indicate statistically significant difference.

## Results

The 38 included patients were evaluated for treatment response. The response rates for the chemotherapy alone group ( $n=20$ ) and the chemotherapy combined with modulated electro-hyperthermia ( $n=18$ ) are summarized in Table III. For patients diagnosed with cervical cancer, the time to relapse following curative treatment was 8.95 months following the first treatment for the chemotherapy only group and 9.16 months for the combined chemotherapy with modulated electro-hyperthermia group. The overall response rate (CR+PR+SD/PD) to treatment was significantly greater in the

group that underwent chemotherapy combined with modulated electro-hyperthermia ( $P=0.0461$ ; Table III).

At the evaluation conducted at the final follow-up visit, the reaction was significantly greater ( $P=0.0218$ ; Table IV) in the group that underwent chemotherapy combined with modulated electro-hyperthermia compared with the group that underwent chemotherapy alone.

In the case of chemotherapy alone, statistically significant recurrence was only observed when the cervix was the target of the therapeutic response ( $P=0.0456$ ), but in the chemotherapy combined with modulated electro-hyperthermia, no significant differences between abdominal lymph node and cervical recurrences were observed ( $P=0.6199$ ). The follow-up period was 7-21 months (mean 11 months) for the chemotherapy only group and the follow-up period was 7-28 months (mean 13.5 months) for the chemotherapy combined with modulated electro-hyperthermia group. The Kaplan-Meier plot of overall survival is presented in Fig. 1. Based on the overall survival rates of the two groups, chemotherapy combined with modulated electro-hyperthermia did not significantly increase disease-free survival compared with chemotherapy alone ( $P=0.235$ ).

The body temperature ranged from 36.4-36.9°C (mean, 36.5°C) prior to treatment and 36.9-38.2°C (mean, 37.6°C) following modulated electro-hyperthermia indicating an average increase of 1.1°C. The temperature of the abdominal skin surface below the upper electrode ranged from 36.4-37.3°C (mean, 36.8°C) prior to heating, and increased to 39.8-41.9°C (mean, 40.8°C), for an average surface temperature increase of ~4°C (Fig. 2).

The majority of patients suffered the following chemotherapy complications: Nausea, vomiting, pancytopenia and peripheral neuropathy. However, severe chemotherapy-related complications did not occur. The side effects included hot sensations and abdominal discomfort for 8/18 (44%) patients, and no other side effects (burns or blisters) were reported. No late toxicity associated with modulated electro-hyperthermia was observed.

The pathological characteristics, chemotherapeutic regimens, cycles, dosages and ages were not significantly different with respect to treatment response.

## Discussion

Surgery, chemotherapy, radiotherapy, or a combination of these modalities continues to be the primary treatment option for invasive cervical cancer. However, following surgery and postoperative radiotherapy, primary definitive concurrent chemo-radiation therapy or radiotherapy alone results in

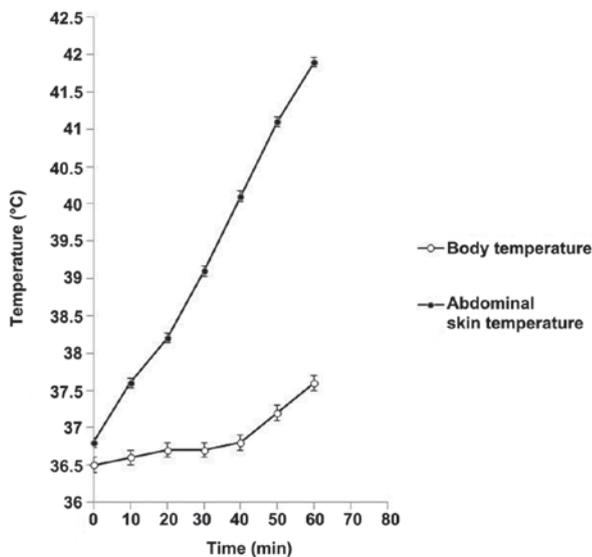


Figure 2. Body temperature and abdominal skin surface temperature underneath the electrode, during modulated electro-hyperthermia.

the development of recurrent pelvic disease in up to 40% of patients. With the exception of salvage surgery as a treatment option for certain individuals among these patients, the use of systemic chemotherapy is the only remaining treatment modality (27). Cisplatin has emerged as the most active single agent for treating patients with metastatic disease, and no other standard cytotoxic drug has been consistently associated with objective response rates of  $\geq 25\%$ . However, for patients who experience relapse following definitive radiation therapy, cisplatin has only a minor effect (6,28).

In a study by Potter *et al* (29), the complete response rate to cisplatin in patients with distant metastases was 53% with an overall response rate of 73%, whereas no complete responses and only 7 partial responses (21%) were observed among 33 patients with localized pelvic recurrence or persistent disease. Thus, the application of deep local hyperthermia along with the systemic administration of cisplatin appears to be an attractive option in patients with recurrent pelvic cervical cancer. Once initial feasibility data regarding the clinical use of cisplatin and local hyperthermia combination treatment were reported (29), Rietbroek *et al* (7) published a phase II study of combined weekly locoregional hyperthermia and systemic cisplatin administration in patients with previously irradiated recurrent cervical carcinoma (30). Using a regimen of 50 mg of cisplatin per week with a one-week interruption following four cycles for a total of 12 cycles, corresponding to a projected dose intensity of 40 mg per week, these authors observed an overall response in 12/23 patients (52%; 95% confidence interval, 31-73%) (7).

The expectation is that a hyperthermia-induced increase in temperature may increase blood flow in the targeted region as a homeostatic response (31,32). An elevated local temperature ( $\leq 40^\circ\text{C}$ ) has been demonstrated to initiate various physical and chemical processes and to ease pain in patients with cancer (27). Drug potentiation in target tissues increases the treatment response. The temperature increase induced by hyperthermia enhances the reaction rate of a given drug independent of an increase in drug delivery due to

enhanced blood flow, and increases the reaction rate in target tumor cells, thereby escalating tumor cell death (18,23). The thermally increased metabolism (the so-called enhanced chemo-metabolism) associated with hyperthermia also increases the absorption of cytotoxins (27) and is expected to enhance drug absorption.

It is well known that heating tumors to mild temperatures, for example  $40\text{--}43^\circ\text{C}$ , kills tumor cells and increases the tumor response of radiotherapy and chemotherapy with various anti-cancer drugs (33,34). The heat-induced increase in the tumor response to radiotherapy is due, at least in part, to an increase in oxygen supply via the heat-induced enhancement of intratumoral blood circulation. The heat-induced increase in the tumor response to chemotherapy may be due to the following three factors. First, mild heating increases the delivery of chemotherapy drugs to tumors by increasing tumor blood flow. Second, mild heating elevates the cellular uptake of drugs by increasing cell membrane permeability. Third, heating facilitates the reaction rate of drugs, which potentiates their cytotoxicity (27). It must be noted that the systemic body temperature may increase when tumors are treated with regional or local hyperthermia (22). It is therefore likely that such an increase in body temperature may alter the pharmacokinetics of chemotherapy drugs when chemotherapy and regional hyperthermia are concomitantly applied (35).

In the present study, concerning cervical cancer recurrence in patients previously treated with irradiation, chemotherapy combined with modulated electro-hyperthermia significantly increased the treatment response. The overall response rate (CR+PR+SD/PD) to treatment was significantly improved among the patients who underwent chemotherapy combined with modulated electro-hyperthermia compared with those that underwent chemotherapy alone ( $P=0.0461$ ). At the evaluation conducted at the last follow-up visit, the results were significantly improved in the group that underwent chemotherapy combined with modulated electro-hyperthermia compared with chemotherapy alone ( $P=0.0218$ ). According to the present study, anti-cancer treatment and hyperthermia may have a synergistic effect.

Specifically, in the case of chemotherapy alone, significant recurrence was observed only when the cervix was the target of the therapeutic response ( $P=0.0456$ ), but in the chemotherapy combined with modulated electro-hyperthermia group, no significant differences in abdominal lymph node and cervical recurrence were observed ( $P=0.6199$ ). Hyperthermia may therefore be slightly more effective for the treatment of abdominal lymph node metastasis.

The present study demonstrated the feasibility and advantages of chemotherapy combined with hyperthermia, concurrent with the application of platinum derivatives, for patients with recurrent cervical cancer who have regional lymph node metastasis. A longer-term follow-up study is required to compare the disease-free survival rates of patients.

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