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Original Article

Efficacy of Combining Radiotherapy and/or Chemotherapy with Regional Hyperthermia on Advanced Cervical Cancer

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ABSTRACT

Background and Aim: Cervical cancer is the seventh most frequent cancer worldwide but more than 80% of cases occur in developing countries. This study was carried out to evaluate the results of combining radiotherapy and/or chemotherapy with regional hyperthermia on advanced cervical cancer (FIGO IIIA~IIIB). **Methods:** The study used new medical instrument was the first step of demonstrating the curative value against cervical cancer in DPR Korea. The medical instrument has been named as Hyperthermia instrument-NAMSUN -413 based on dielectric heating principle. **Results:** After Hyperthermia (HT group) and irradiation (TRT group) alone, 0% and 2.3% of patients showed complete response (CR) respectively, but in thermochemotherapy (HT+CT group) and thermoradiotherapy (HT+TRT group) CR rate increased to 23.5% and 25.0% respectively. HT+CT and HT+TRT during the treatment resulted in the acceptable side effects due to cisplatin or irradiation. **Conclusion:** As a result of our data, hyperthermia, as an adjuvant with radiation and chemotherapy can be used to treat the advanced cervical cancer.

Keywords: Regional hyperthermia, Radiotherapy, Chemotherapy, Advanced cervical cancer.

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INTRODUCTION

Among all the treatments, hyperthermia has shown potentialities to be applied as alternative therapy or adjunctive therapy with established cancer treatments.[1] In recent times, the first official clinical use of hyperthermia was in the early part of the 20th century, when it was used as a treatment for cervical cancer.[2] However, it was not until the 1970s that the modern discipline of thermotherapy really emerged beyond the regime of experimentation.[3-5] Nevertheless, due to limits in technological advances, very few clinical studies were performed before the 1990s. However, by the turn of the 21st century, there was a renewed interest in hyperthermia research and clinical applications in local and regional hyperthermia.[6-9] Similar to other treatment modalities, hyperthermia's clinical objective is to achieve the localized death of tumorigenic tissue without damaging the surrounding normal tissue. In the last decade progress in gynecological oncology has been achieved mainly by new cytotoxic drugs and advances in radiation technology. When possible, surgical removal, in combination with other treatment modalities, often offers the best prognosis for patients.[10] However, common treatment modes such as radiotherapy and chemotherapy are known to induce multiple side effects that can have long-lasting impact on a patient's quality of life[11] and hormonal therapy is only available to patients with certain types of cancer.[12] There has been increasing interest in hyperthermia as a treatment modality because it has minimal side effects and potential synergistic effects when used in combination with radiotherapy and chemotherapy.[13,2]

MATERIALS AND METHODS

Patients

We recruited 124 inpatients from radiation medical institute of Medical Research Academia, Pyongyang, DPR Korea. The age range was between 33-69 years and average age was 47.6 years. They were diagnosed as IIIA~IIIB according to FIGO classification. The study was approved by the ethics committee of Pyongyang University of Medical Sciences and all patients gave their oral and written informed consent to participate.

Hyperthermia Instrument-NAMSUN-413

Hyperthermia instrument named as NAMSUN-413 was purchased from Pyongyang Medical Instruments Company, DPR Korea and certified by the National Board of Medical Instruments

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Certification. The instrument consists of 5 main parts: dielectric heating guidance system, thermocouple temperature sensor, body of machine, cooling water circulation device and monitor screening.

Administration of Hyperthermia Instrument

Pelvic of patients was put into dielectric heating guidance system and maintained a correct posture and steady state. Then through vagina thermocouple temperature sensor was located in uterine cervical cancer and the temperature of superficial tumors was measured before heating procedure. After the instrument moved, temperature of tumor area was achieved at 42.5~43°C within 5 min and the patients received this hyperthermia for 60~90min once a week over a period of 6 weeks (HT group).

This therapy was combined with radiotherapy and/or chemotherapy.

Hyperthermia Combined with Irradiation

The patients were irradiated with ^{60}Co gamma-rays (Teleradiotherapy, TRT). TRT (TRT group) was based on one fraction of 2.0 Gy per day and a total dose of 60 Gy during 6 weeks. In HT+TRT group, the patients received hyperthermia within 2 hr after TRT.

Hyperthermia Combined with Chemotherapy (HT+CT group)

Chemotherapy with cyclophosphamide (500 mg/m^2, iv, every 3 weeks) and cisplatin (50 mg/m^2, iv, every 3 weeks) was administered receiving hyperthermia.

Response and Toxicity Evaluations

The response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) after combining therapy for 6 weeks. A Complete Response (CR) was defined as the disappearance of all target and non-target lesions and no new lesions being documented. A Partial Response (PR) was defined as at least a 30% decrease in the sum of the longest dimension of the target lesions, which was also documented. Overall Response (OR) was defined as the sum of CR and PR. Stable Disease (SD) implies that none of the above applies. Progressive Disease (PD) was defined as a 20% increase in the longest dimension of the sum of the target lesions or the development of new lesions. Toxicity related to treatment was graded according to the NCI Common Terminology Criteria for Adverse Events, Version 3.0. For patients who had been treated before the introduction of RECIST or NCI Common Terminology Criteria for Adverse Events, Version 3.0., information related to disease status and toxicity were collected, and response rate and toxicity were retrospectively reevaluated according to these criteria.

Statistical Analysis of Data

The differences between the groups with respect to stage, histology, site of recurrence, and prior treatment were assessed using the Fisher's exact Test. Response, toxicities and survival rate were also compared using Fisher's exact Test.

RESULTS

As shown in Table 1, in the groups of HT+CT and HT+TRT overall response rates were respectively 93.3% (28/30) and 97.5% (39/40), while were respectively 70% (7/10) and 88.7% (39/44) in the groups of HT and TRT. PR was achieved in most of the patients, but CR was 0% in only HT group. On the order hand, in the groups of HT+CT and HT+TRT, 2 patients (6.7%) and 1 patient (2.5%) demonstrated SD respectively.

As shown in Table 2, in HT group any toxicity were not observed, and in HT+CT, TRT and HT+TRT groups grade 3 toxicities observed were mainly fatigue and maldigestion such as anorexia and vomiting. Although grade 1-3 toxicities were commonly observed in all groups except HT group, there were no grade 4 toxicities including hematologic, gastrointestinal, neurologic toxicities etc. In HT+CT, TRT and HT+TRT groups most toxicities were limited at the ranges of grade 1-2 and the percentage of grade 3 toxicity among these groups was lower than 7%.

Table 3 showed that 4 of 12 patients (33.3%) were alive for 5 years in TRT group, and in HT+TRT group the 5-year survival rate was 46.7% and this was lower than the 3-year's (53.3%). On the order hand, among the patients that were treated with TRT+BT 15 of 32 patients (46.9%) were alive for 5 years.

One month later after beginning of TRT 32 of 44 patients treated with TRT were received BT by standard form and thus they became TRT+BT group. 2~3 months later after treatment 10 of 40 patients treated with HT+TRT received BT by non-standard form voluntarily and thus they were excluded from this group.

Table 1: Objective response.

	N	OR (CR+PR) (%)	SD (*n*, %)	PD (*n*, %)
HT	10	70(0+7/10)	30(3/10)	0
HT+CT	30	93.3(7+21/30)	6.7(2/30)	0
TRT	44	88.7(1+38/44)	11.3(5/44)	0
HT+TRT	40	97.5(10+29/40)	2.5(1/40)	0

HT: Hyperthermia; CT: Chemotherapy; TRT: Teleradiotherapy.

Table 2: Toxicities.

	N	Grade 1	Grade 2	Grade 3	Grade 4
HT	10	0	0	0	0
HT+CT	30	19(63.3)	10(33.3)	1(3.4)	0
TRT	44	25(56.8)	16(36.4)	3(6.8)	0
HT+TRT	40	25(62.5)	13(32.5)	2(5.0)	0

HT: Hyperthermia; CT: Chemotherapy; TRT: Teleradiotherapy.

Table 3: Survival rates in TRT and HT+TRT group

	N	Total dose (gray)	3-year (%, *n*)	5-year (%, *n*)
TRT	12	60	33.3(4)	33.3(4)
HT+TRT	30	60	53.3(16)	46.7(14)
TRT+BT	32	80-90	46.9(15)	46.9(15)

BT: Brachytherapy; HT: Hyperthermia; TRT: Teleradiotherapy.

DISCUSSION

In the last decade progress in gynecological oncology has been achieved mainly by new cytotoxic drugs and advances in radiation technology. Radiotherapy is the major treatment modality for invasive cervical cancer and can achieve a good treatment outcome in patients with early-stage disease. However, substantial treatment failure has been reported to occur in patients with advanced disease.[14]

Historically, cisplatin has been the most active single agent for recurrent cervical cancer. However, its response rate has been generally low, varying from 17% to 38% with a response duration of 3 to 6 months.[15] In order to improve survival, various studies have evaluated the survival benefit of adding other cytotoxic agents to cisplatin. Hyperthermia, as an adjuvant with radiation and chemotherapy, has shown promise in the treatment of cancer. Efficacy of local and systemic therapy can be increased by combining radiotherapy and/or chemotherapy with Locoregional Hyperthermia (LRH). Increasing the temperature of the target tissue up to 41-43°C leads to local hyperemia and the tumor tissue becomes more responsive to cytotoxic interventions. In several prospective randomized studies, the combination between LRH and radiotherapy was superior to radiotherapy alone in terms of local control (e.g. chest wall recurrence in breast cancer) and has led to longer overall survival in advanced cervical cancer. Platinum derivatives and other cytotoxic drugs have shown synergistic effects with LRH and the combination of both has elicited high response rates in recurrent cervical cancer.[16] Despite of the fact, that the available data are still preliminary, the inclusion of LRH into multimodal cancer therapy concepts appears to be very promising. In the current study, we have demonstrated that hyperthermia, as an adjuvant with radiation and chemotherapy is active in patients with the advanced cervical cancer. The response rates were respectively 93.3% and 97.5% after treatment of HT+CT and HT+TRT for 6 weeks and there was no significant difference in response rate between these groups. But response rates of HT and TRT were respectively 70% and 88.7%, which were consistent with previous own experiences. When compared with other groups, HT+TRT was superior in OR and inferior in SD. Moreover, HT+TRT showed higher in 3 and 5-year survival rates compared to TRT. In all of group's PD was not observed. In addition to using a less toxic regimen, it is also important to maintain a patient's quality of life. Although grade 1-3 toxicities were commonly observed in all groups except HT group, there were no grade 4 toxicities including hematologic, gastrointestinal, neurologic toxicities etc. In HT+CT, TRT and HT+TRT groups most toxicities were limited at the ranges of grade 1-2 including anorexia and vomiting, and the percentage of grade 3 toxicity among these groups was lower than 7%. As a result of our research, 4 of 12 patients (33.3%) were alive for 5 years in TRT group, and in HT+TRT group the 5-year survival rate was 46.7% and this was lower than the 3-year's (53.3%). On the order hand, among the patients that were treated with TRT+BT 15 of 32 patients (46.9%) were alive for 5 years.

CONCLUSION

Our data demonstrates that the combination of radiotherapy and/or chemotherapy with hyperthermia is effective in the patients with the advanced cervical cancer. This study provides that hyperthermia as an adjuvant with radiation and chemotherapy may be useful for treatment of the advanced cervical cancer. Well-designed comparative studies are still needed to evaluate the role of hyperthermia as an adjunct to conventional cancer therapy. However, we believe that our encouraging results are enough to warrant further investigation of hyperthermia in a future randomized controlled trial as a treatment for the advanced cervical cancer.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

HT: Hyperthermia Group; **TRT:** Teleradiotherapy Group; **CR Group:** Complete Response Group; **RECIST:** Response Evaluation Criteria in Solid Tumors; **PR:** Partial Response; **OR:** Overall Response; **SD:** Stable Disease; **PD:** Progressive Disease; **LRH:** Locoregional Hyperthermia.

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