Preliminary Study of the Combination of Radiation Therapy, Chemotherapy, and Hyperthermia in Stage IIIB Cervical Carcinoma

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Abstract: We have planned to start a randomized trial in which concurrent chemotherapy add to radiotherapy, concurrent hyperthermia add to radiotherapy, and combining all these three modalities for advanced cervical carcinomas.

In this preliminary study, we evaluated the clinical response and acute toxicity for three patients with FIGO Stage IIIB cervical carcinomas treated with combining all these three modalities. A complete response was achieved in 2 patients, and partial response in one patient. Grade 3 leukopenia occurred in 2 patients, Grade 2 in one patient. Grade 1 gastrointestinal and genitourinary toxicity were found in all patients. However, none of the patients had Grade 4 toxicity. Treatment with concurrent chemotherapy and hyperthermia add to definitive radiotherapy was shown to be effective in patients with FIGO Stage IIIB cervical carcinoma. In addition, a combination of all three modalities was well tolerated and had acceptable acute toxicity.

Key Words: stage IIIB cervical carcinoma, combination treatment, preliminary study, response, acute toxicity

Introduction

Cervical cancer is one of the most common tumors affecting women worldwide, both in incidence and mortality1), and approximately 5,000 women die of this disease each year in Japan. Radiotherapy (RT) is widely accepted as the treatment of choice for patients with International Federation of Gynecology and Obstetrics (FIGO) Stage IIIB carcinoma of the cervix. There have been no substantial improvements in the treatment of cervical cancer since the advent of mega voltage irradiation in the 1950s2). Some clinicians have tried a number of experimental treatments designed to enhance the response of tumors to RT: neutrons, radiation sensitizers, and chemotherapy delivered intra-arterially3). Most these approaches have failed to improve the results over treatment with radiation alone4).
Among five randomized trials demonstrating better results for patients with advanced cervical cancer by adding cisplatin to RT summarized by Thomas\(^2\), only one trial reports on the results of patients with FIGO Stage III-IV (n = 118)\(^4\). However, overall survival was not improved for FIGO Stage III-IV patients in that study.

More recently, the results of trial by Dutch group\(^5\) demonstrated an increase in 3-year overall survival, from 27% to 51%, by adding hyperthermia (HT) to RT for cervical carcinoma patients in FIGO Stage IIB-IVA. We also reported that the 3-year overall survival and disease-free survival of patients in FIGO Stage IIIB treated with thermoradiotherapy (TRT) (58.2% and 63.6%) were better than those of patients treated with RT (48.1% and 45%), but the difference was not significant\(^6\). The 3-year local relapse-free survival of patients treated with TRT (79.7%) was significantly better than that of patients treated with RT (48.5%).

Both concurrent chemotherapy and concurrent HT add to RT in cervical cancer, and therefore, combination of all these three modalities might lead to increased response rates and disease-free and overall survival. We have planned to start a randomized trial employing concurrent chemotherapy add to radiotherapy (CRT), concurrent hyperthermia add to radiotherapy (TRT), and combination of all these three modalities (CTRT) for advanced cervical carcinomas to confirm this hypothesis.

In this preliminary study, we evaluated the clinical response and acute toxicity of FIGO Stage IIIB cervical carcinomas patients treated with CTRT.

Materials and Methods

Between February 2001 and April 2001, 3 patients with FIGO Stage IIIB carcinoma of the uterine cervix were treated with CTRT at Kansai Medical University.

The patient eligibility criteria for entry into the study were as follows: (1) histologically proven cervical carcinoma at FIGO Stage IIIB, (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, (3) no prior chemotherapy, radiotherapy, or surgery, (4) adequate bone marrow, liver, and renal function, (5) no concomitant malignancies, and (6) informed consent. In addition, patients with pacemakers or those with subcutaneous fatty layer exceeding 4 cm were considered as not eligible for this study. The patients' demographics and tumor characteristics are noted in Table I.

Table I. Characteristics of the patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>PS</th>
<th>Histology</th>
<th>Size (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>0</td>
<td>Adenocarcinoma</td>
<td>4.5</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>0</td>
<td>Squamous cell carcinoma</td>
<td>6.6</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>2</td>
<td>Squamous cell carcinoma</td>
<td>6.5</td>
</tr>
</tbody>
</table>

PS, performance status.

All patients entered in the protocol were treated with external pelvic RT using a 6 MV linear accelerator. The pelvic field extended from the upper margin of L5 to the midportion of the obturator foramen or the lowest level of disease, with a 4 cm margin, and laterally 2 cm beyond the lateral margins of the bony pelvic wall. A total of 30.6 Gy was targeted to the whole pelvis, with an additional dose to the parametria with central shielding for a total of 52.2 Gy. The fractions were 1.8 Gy daily, given
Combination treatment in Stage IIIB cervical carcinoma.  • Y.Harima et al.

5 days/week. In addition, iridium 192 high-dose-rate brachytherapy was given in fractions of 7.5 Gy once per week for a total of 30 Gy to point A.

HT was delivered via a radiofrequency capacitive heating device (Thermotron RF-8, Yamamoto Vinita Co., Osaka, Japan), which uses 8 MHz radiofrequency electromagnetic waves as a source of heat. The output power ranged from 800 to 1500 W. The heating was performed as previously described7). The electromagnetic power was applied between two external disk electrodes 25 and 30 cm in diameter placed on opposite sides of the pelvic region. The temperature of the tumor was measured in all patients by using a 4-point microthermo couple-sensor, which was inserted in advance into the tumor and rectum through a 21-gauge catheter, and left until the end of last HT session. HT was usually applied within 30 min after external RT for a total of 60 min independent of the pattern of temperature elevation once a week for a total of 5 sessions. The first heating was usually performed after the third or fifth fraction of external RT.

We defined the maximum tumor temperature (T max) as the maximum temperature obtained in the tumor during the steady state and at the end of treatment. The steady state was defined at 20 min after the start of HT.

All patients received an intravenous infusion of 40 mg of cisplatin per square meter of body-surface area over a 4-hour period once a week concomitant with RT and HT. Our treatment schedule combining all these three modalities for FIGO Stage IIIB cervical carcinomas was shown in Fig. 1.

![TREATMENT SCHEDULE](image)

**Fig. 1.** Treatment schedule. A total of 30.6 Gy was targeted to the whole pelvis, with an additional dose to the parametria with central shielding for a total of 52.2 Gy. Iridium 192 high-dose-rate brachytherapy was given in fractions of 7.5 Gy once per week for a total of 30 Gy to point A. Hyperthermia was applied within 30 min after external radiotherapy once a week for a total of 5 sessions. All patients received an intravenous infusion of 40 mg of cisplatin per square meter once a week for a total of 5 times during radiotherapy and hyperthermia.

The response of the tumor to the treatment was evaluated as follows: complete response (CR) when no tumor was detected by physical examination or magnetic resonance imaging and cytologic or biopsy studies were negative for malignant cells for at least 1 month after treatment; partial response (PR) when the tumor mass was reduced by ≥ 50%; no change (NC) when the reduction in the tumor mass was < 50%.

Toxicities were scored according to a modification of the Radiation Therapy Oncology Group (RTOG) morbidity scale9). Patients were examined every month after treatment.
Results

Treatment was completed according to the schedule in all 3 cases. Initial response was CR in two cases (case 2, and case 3), and PR in one case, (case 1). At present, all patients are alive and well.

Grade 3 leukopenia occurred in 2 patients, Grade 2 in one patient. Grade 1 gastrointestinal and genitourinary toxicity were found in all patients. None of the patients had Grade 4 toxicity.

Table II. Side effects during treatment or within 60 days after the completion of treatment

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Grade</th>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>Hematologic</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Genitourinary</td>
<td></td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cutaneous</td>
<td></td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>1</td>
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<td>Weight loss</td>
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<tr>
<td>Fever</td>
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<td>3</td>
<td>0</td>
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</tr>
</tbody>
</table>

Toxicities were scored according to a modification of RTOG morbidity scale.

The thermometry results for FIGO Stage IIIB cervical cancer cases demonstrated a maximum tumor temperature (T max) of 41.2°C in case 1, 40.8°C in case 2, and 41.5°C in case 3. There was no correlation between temperature and initial response.
Discussion

There is no curative surgical option for patients with locally advanced invasive carcinoma of the uterine cervix. Neither adjuvant surgery nor increasing doses of radiotherapy alone are likely to increase the rate of pelvic control in patients without the consequence of increased early and late complications\(^9\). In our previous clinical study, TRT for patients with FIGO Stage IIIB cervical carcinoma proved to be a promising treatment with respect to the local control rate (P = 0.048) and the 3-year local relapse-free survival (P = 0.048)\(^6\). However, the late effects of TRT in such patients have been controversial, as evident from earlier clinical trials\(^5\)\(^-\)\(^12\). Our previous results are in agreement with those reported by Sharma et al.\(^12\), Datta et al.\(^11\), and Van der Zee\(^5\) who have shown improvement of both local control rate and survival by TRT. Datta et al.\(^11\) reported improvement by adjuvant HT of a local control and survival in patients with Stage IIIB uterine cervix carcinoma. Sharma et al.\(^12\) showed better local tumor control for Stage II and III cervical carcinoma with the help of regional HT in a randomized trial. More recently, the results of trial by Van der Zee et al.\(^5\) have also demonstrated an increase in 3-year overall survival, from 27% to 51%, by adding HT to RT for cervical carcinoma patients. In contrast to both reported in this paper and above mentioned others' findings, Hornback et al.\(^10\) reported earlier that although tumor control was superior when patients underwent regional HT, 5-year survival was not statistically affected by HT. Notably, former study was not randomized. We also did not observe increased rate of distant metastases in contrast to data being reported by Sharma et al.\(^12\).

A way to improve the treatment outcome by combining RT with chemotherapy has been reported by Wong et al.\(^13\). They demonstrated for stage I, II, and III cervical cancer that chemoradiation (epirubicin 60 mg/m\(^2\)) followed by adjuvant chemotherapy with epirubicin 90 mg/m\(^2\) administered at 4-week intervals for five additional cycles resulted in a significantly longer disease-free (P = 0.03) and cumulative survival (P = 0.04) as compared to standard pelvic RT. Moreover, the rate of distant metastasis was decreased (P = 0.012), although there was no difference in long-term local tumor control (P = 0.99).

On the other hand, the Gynecologic Oncology Group\(^4\) has explored the role of RT and concurrent chemotherapy with hydroxyurea, cisplatin and 5-fluorouracil. In their study, the rate of local recurrences was significantly lower with cisplatin-based regimen, whereas the rate of distant recurrences was only slightly reduced. These results suggested that the principal effect of cisplatin is radiosensitization. Morris et al.\(^4\) also reported that the addition of chemotherapy improved the control of pelvic disease and significantly increased overall survival rate (P = 0.004). However, as the most important problem, it is unclear whether the results of this study are applicable to all stages of cervical cancer, since only 30 percent of the patients had stage III or stage IVA disease. An improvement with respect to overall survival was not demonstrated for these FIGO Stage III-IV patients (P = 0.44).

HT-induced toxicity was previously reported by Nishimura et al.\(^14\), who suggested that radiation-induced intestinal damage was enhanced by regional HT in patients with locally advanced colorectal cancer. Small bowel obstruction, intestinal fistula, and intestinal perforation were reported to increase in 2% to 19% of the patients with deep-seated malignant tumors by addition of regional HT to RT\(^15\). In our previous report\(^6\), 2 of 20 patients treated with TRT had Grade 3 toxicity. One patient had diarrhea

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(13)
during treatment and developed a sigmoid-ileum fistula 2 years after completing treatment. The second patient developed a colon obstruction 1.5 years after treatment.

The late toxicity of combined RT and cisplatin may be larger than that of RT alone. In a mouse model, an increase in bladder toxicity was found from adding cisplatin to radiotherapy\(^{16}\). In clinical studies, comparing RT alone with RT and carboplatin plus 5-fluorouracil or etoposide, late morbidity was higher in the combined treatment arm\(^{17}\). Based on the clinical trials on cervical cancer, an enhancement of late morbidity was not evident. However, the numbers of patients may be small, and follow-up time too short to demonstrate any difference.

**Conclusion**

Treatment with CTRT was shown to be effective in patients with FIGO Stage IIIB cervical carcinoma. In addition, a combination of all three modalities was well tolerated and had acceptable acute toxicity.

In order to explore the possibilities of further improvements in the treatment of cervical cancer, we have initiated in a study investigating whether CRT, TRT, and CTRT are feasible regimens.

**References**


Combination treatment in Stage IIIB cervical carcinoma. • Y. Harima et al.


子宮頸癌 IIIB 期に対する CDDP 併用
温熱放射線療法の初期治療経験

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要　旨：我々は進行期子宮頸癌の予後を改善するために温熱放射線療法 (TRT), シスプラチン (CDDP) 併用放射線治療 (CRT), CDDP 併用温熱放射線療法 (CTRT) の 3 群の無作為臨床試験を計画した。この臨床試験に先駆けて, CTRT の初期治療効果と副作用について検討した。対象は 2001 年 2 月～4 月までに治療開始した子宮頸癌 IIIB 期で、2 例が扁平上皮癌、1 例が腺癌であった。骨髄、肝、腎機能は正常で、一般状態は良好であった。放射線療法は外部照射と高線量率腔内照射を施行した。CDDP40mg/m²施行後 1 時間以内に放射線。続いて温熱を計 5 回/5 週施行した。治療後 1 ヶ月の抗腫瘍効果は扁平上皮癌の 2 例が CR であったが、腺癌の 1 例は PR であった。2 例に Grade 3, 1 例に Grade 2 の白血球減少を認めたが、他の副作用は Grade 1 以下であった。CTRT は抗腫瘍効果が良好で、急性期副作用も軽度であること示唆された。