Ten Cases of Advanced Uterine Cervical Carcinoma Treated by Radiohyperthermia and Followed over Five Years

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Abstract: The treatment of locally or regionally advanced carcinoma of the uterine cervix is still controversial. We present here ten advanced primary cases of uterine cervical squamous carcinomas treated between 1991 to 1992. The pelvic doses were 54.7 ± 3.8 Gy externally and 25.7 ± 2.7 Gy (point A) intracavitary. Hyperthermia (HT) was performed using a Thermotron RF8, and the effective heating times (>41 ºC) was 202.4 ± 44.0 min / 6.6 ± 0.8 sessions. The mean over-all treatment period was 59.4 ± 8.8 days. Acute adverse effects were observed in two patients, including umbilical burning and a subcutaneous consolidation cranial to the pubic bone. All the stage III patients (N = 7) were locally controlled during their follow-up period. The overall 5-year survival rates for stages III and IVa (N = 3) were 50% and 33%, respectively. The later results were relatively good in patients who did not develop hematogenous metastasis.

The treatment administered was effective for the local control of stage III disease, but not for systemic control. Therefore, a new protocol for radio-chemo-hyperthermia is necessary for improving the survival rates.

Key Words: radiohyperthermia, cervical carcinoma, long-term follow up

Introduction

Radiotherapy for uterine cervical cancer is well established. However, for advanced cancer, the cure rate by radiotherapy is still unsatisfactory, and various combination methods have been proposed1-11). Radiohyperthermia has been reported to increase the local control rate. However, its effects on late results have been controversial13-40.

We evaluated the local control rate and the mechanisms of recurrence - metastasis in 10 patients with advanced cervical cancer who had undergone radiohyperthermia more than 5 years earlier, and discussed the effects, limitations, and the prospect of radiohyperthermia.

Patients and Methods

During 2 years from July, 1991, when this hospital was established, radiohyperthermia was performed in 74 patients (459 sessions), of whom 14 had uterine cervical cancer. Ten of the 14 patients (7 patients with
stage IIIb cancer and 3 with stage IVa cancer) underwent initial treatment. Their mean age was 63.4 ± 6.2 years, and the tumor was histologically squamous cell carcinoma in all patients.

Whole pelvis external irradiation was performed at a daily dose of 1.8 Gy (total 50.4 Gy/28 fractions (fs)) in principle using a Microtron 14 MVX. Depending on the patient, pendular irradiation was added to the parauterine tissue. Whole pelvic irradiation was performed 5 times a week until the initiation of intracavitary irradiation but 3 times a week using a central shield after the initiation of intracavitary irradiation. Intracavitary irradiation using a cobalt source was performed at point A at a dose of 4 Gy twice a week during the same period for the whole pelvic irradiation using a central shield 3 times a week. Thermotherapy was performed using a Thermotron RF8 for 60 min once a week or for 40 min twice a week. No chemotherapy was performed simultaneously with thermotherapy. The heating temperature was measured on each occasion at the deepest site of the vagina using a thermocouple thermometer. Heat sensation in the skin was reduced using an overlay bolus and echo jelly · gauze.

Treatment effects were evaluated according to the criteria of the Cancer Treatment Association. The response rate was defined as the ratio of patients showing a CR or PR to all patients. The survival rate was calculated by Kaplan-Meier’s method.

**Results**

1. **Irradiation and heating**

Tables I and II show the treatment methods and results. The dose of pelvis irradiation was 50.4 - 62.4 Gy (mean, 54.7 ± 3.8 Gy), and that of intracavitary irradiation was 20.0 - 32.0 Gy (mean, 25.7 ± 2.7 Gy). Thermotherapy was performed 6.6 ± 0.8 times, and the total effective heating time (> 41°C) was 202.4 ± 44.0 min. The total intracavitary irradiation dose was 32 Gy in 2 patients in whom vaginal cavity irradiation (4 Gy/0.5 cm) was added. The effective heating time was very short in 1 patient, which was because both heating and measurement of the temperature were difficult due to slight dementia. The total radiothermotherapy period was 59.4 ± 8.8 days and was relatively long in the 2 patients with stage IVa cancer because of suspension and a reduction in the single dose due to development of a vesicovaginal fistula.

| Table I. Patients and Radiotherapy | | |
|------------------------------|------------------|------------------|------------------|-------------------|
| **case** | **Age [y.o.]** | **Stage** | **ERT* [Gy]** | **ICRT* [Gy]** | **Period [day]** |
| 1 | 51 | IIIb | 62.4 | 20.0 | 67 |
| 2 | 56 | IIIb | 61.8 | 32.0 | 61 |
| 3 | 64 | IIIb | 50.8 | 24.0 | 49 |
| 4 | 67 | IIIb | 60.8 | 24.0 | 58 |
| 5 | 67 | IIIb | 50.4 | 24.0 | 50 |
| 6 | 75 | IIIb | 50.4 | 24.0 | 49 |
| 7 | 78 | IIIb | 57.4 | 25.0 | 51 |
| 8 | 56 | IVa | 50.4 | 32.0 | 86 |
| 9 | 58 | IVa | 52.2 | 24.0 | 51 |
| 10 | 62 | IVa | 50.6 | 28.0 | 72 |
| mean | 63.4 | | 54.7 | 25.7 | 59.4 |
| medium | 63.0 | | 51.5 | 24.0 | 54.5 |
| 95%CI | 6.2 | | 3.8 | 2.7 | 8.8 |

*ERT: External radiotherapy, **ICRT: Intracavitary radiotherapy
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2. Local effects

In all patients with stage III cancer, a CR was obtained. However, in the 2 patients with stage IVa cancer showing prolongation of the total treatment period, adequate effects could not be observed, and only a PR was obtained. In these patients, since a vesicovaginal fistula developed during the treatment, the irradiation dose was lower than that routinely used for stage IVa. Thus, the response rate was 100%. In the patients showing a CR, no local recurrence in the uterus was observed during the course.

3. Late results

As Table II shows, the entire course could be followed up in all patients except 1. The mean follow-up period was 43.7 months. The 5-year survival rate was 50% for stage III and 33% for stage IVa. However, since the number of the subjects was small, these figures were considered to be only reference values because the confidence interval was wide as shown by the range of errors expressed as the standard deviation. Concerning the association between the development mechanism of metastases and prognosis (Table IV), the late results were relatively good in patients who did not develop hematogenous metastasis ($P = 0.07$).
4. Acute side effects of thermotherapy

Almost all patients developed heat sensation in the skin and slight pain in some sessions. In 1 patient, umbilical burn injury occurred, but thermotherapy could be continued without suspension using Xylocaine gauze. In another patient, subcutaneous induration was observed on the oral side of the pubic bone. In this patient, subcutaneous fat was thick, and treatment could be performed after a 2-week suspension period using a physiological saline pad (Table III).

Discussion

Radiotherapy for uterine cancer has reached the limitations in terms of irradiation techniques\(^1\). However, for advanced cervical cancer, satisfactory cure rates have not been obtained by radiotherapy, and other methods such as chemotherapy have been used in combination with radiotherapy\(^9,10\). Thermotherapy is a useful method for intractable advanced cancer. The JASTRO Thermotherapy Research Group, which analyzed the effects of thermoradiotherapy for cervical cancer, found increases in the local control rate and the survival rate\(^9\).

The effects of thermoradiotherapy on the local control of cervical cancer may have been established, but its effects on late results have still been controversial\(^3,7\). In this study, we evaluated 10 patients 5 years or more after the initiation of thermotherapy and observed satisfactory local effects at least in the stage III patients. However, no significant effects on late results were observed. Our results suggested that the prognosis is markedly affected by the presence or absence of distant metastasis. This problem can not be coped with thermoradiotherapy that is originally local therapy. In the stage III patients, no local recurrence was observed, indicating adequate local control. Therefore, methods or controlling distant metastasis are necessary.

The course of the patients who died of cancer was evaluated in terms of distant metastasis. These patients died of distant metastasis of cancer 1 - 3 years after the initiation of treatment. Though the possibility of induction of metastasis by thermotherapy can not be excluded, it is more likely that
subclinical metastatic lesions were already present at the time of treatment. If so, prophylactic systemic chemotherapy is necessary. Attempts of thermo-chemo-radiotherapy have already been performed, and "prophylactic" in these attempts indicates relatively mild chemotherapy that can be used in combination with thermoradiotherapy. The late results of at least stage III cancer may be markedly improved by the combination between standard radiotherapy used for stage II cervical cancer and mild thermochemotherapy because of its established local effects and the control of distant metastasis by chemotherapy.

Based on these principles, we perform thermo-radio-chemotherapy according to the following protocol: thermochemotherapy, 60-min heating once a week with Paraplatin (100 mg); radiotherapy, whole pelvis 4-port irradiation 5 times a week (25.4 Gy/14 fs) followed by the combination between pelvic irradiation with a central shield 3 times a week (25.4 Gy/14 fs) and intracavitary irradiation (point A, 4 Gy) using a cobalt source 2 times a week (total 7 times) during the same 4-week period. Though this therapy has adequate local effects, we have not reached a conclusion concerning its effects on late results.

Thermoradiotherapy for uterine cervical cancer has marked local effects, but its effects on late results have been suggested to be questionable. This indicates the limitations of thermoradiotherapy that is originally local therapy. We evaluated patients who underwent thermoradiotherapy at our institution and suggested the usefulness of prophylactic chemotherapy for improving prognosis. Concerning prophylactic chemotherapy, we consider relatively mild chemotherapy that is used in thermoradiochemotherapy. Excellent results have already been reported by this method. However, further studies are necessary to reach a conclusion.

References

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温熱併用放射線治療後5年以上経過した子宮頸癌III・IVa期症例
10例の検討

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要  旨：1991～2年に当院で温熱放射線療法をおこなった10例の子宮頸癌進行例初回治療例を対象に局所制御率・長期予後に頼り検討を加えた。骨盤照射54.7±3.8 Gy，腔内照射25.7±2.7 Gyに加え，有効加温時間202.4±44.0分／6.6±0.8回の温熱療法が施行された。III期症例（N=7）はすべてCR，5年生存率はIII期50％，IVa期33％と算出された。血行転移非出現例が，比較的予後良好の傾向がある（p=0.07）。III期症例では局所の制御能は十分であると思われ，遠隔転移の制御が次なる課題であり，予防的化学療法が予後改善に対して可能性を有すると考える。