Int. J. Radiation Oncology Biol. Phys., Vol. 61, No. 1, pp. 145–153, 2005

0360-3016/05/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2004.04.057

CLINICAL INVESTIGATION **Cervix**

REGIONAL HYPERTHERMIA COMBINED WITH RADIOTHERAPY FOR UTERINE CERVICAL CANCERS: A MULTI-INSTITUTIONAL PROSPECTIVE RANDOMIZED TRIAL OF THE INTERNATIONAL ATOMIC ENERGY AGENCY

ARUMUGAM VASANTHAN, M.D.,* MICHIHIDE MITSUMORI, M.D.,† JEONG HO PARK, M.D.,‡ ZENG ZHI-FAN, M.D.,§ ZHONG YU-BIN, M.D.,‖ PRASKOVYA OLIYNYCHENKO, M.D.,¶ HIDEO TATSUZAKI, M.D.,** YOSHIAKI TANAKA, M.D.,†† AND MASAHIRO HIRAOKA, M.D.†

*Department of Radiation Oncology, Cancer Institute, Chennai, India; †Department of Therapeutic Radiology and Oncology, Kyoto University Graduate School of Medicine, Kyoto, Japan; ‡Department of Radiation Oncology, Mary Knoll Hospital, Pusan, South Korea; §Department of Radiation Oncology, Sun Yat-sen University of Medical Sciences, Guangzhou, China; ‖Department of Radiation Oncology, China-Japan Friendship Hospital, Beijing, China; ¶Kiev City Oncology Centre, Kiev, Ukraine; **National Institute of Radiological Sciences, Chiba, Japan; ††Department of Radiology, Nihon University School of Medicine, Tokyo, Japan

Purpose: Hyperthermia can be used to enhance the effects of radiation, and a combined treatment may, in some circumstances, be an advantage. Uterine cervical cancer is very common in developing countries. The control of locally advanced pelvic tumors is difficult with conventional treatment modalities. Based upon the biologic rationale and in view of the recent advances in heating and thermometry techniques, radiotherapy in combination with hyperthermia was investigated in a multi-institutional prospective randomized trial sponsored by the International Atomic Energy Agency. The primary purpose was to clarify whether the combination of hyperthermia and radiotherapy improves the rate of local control, compared with radiotherapy alone.

Methods and Materials: A total of 110 patients with biopsy-proven, locally advanced carcinoma of the uterine cervix were randomized to treatment by radiotherapy with or without hyperthermia. The patients were stratified by institution, stage, and histologic type. Each patient received external beam radiation therapy and brachytherapy. For the patients randomized to receive hyperthermia, a minimum of five sessions (60 min each, once per week) were administered, employing a radiofrequency (RF) capacitive heating device. Intratumoral temperature was measured at the first hyperthermic treatment, and at least once more during the course of treatment. The equipment and the policies and procedures at each participating institution except one (Pusan) were personally inspected at least once by the corresponding author, to ensure that quality assurance procedures were in place and were followed for treatment according to the protocol guidelines. The median follow-up period was 466 days for all the patients and 512 days for the surviving patients.

Results: The two arms were well balanced with regard to the patient factors, tumor factors, and treatment factors. The overall survival rate at 3 years was 73.2%, and the local control rate was 68.5%. There were no significant differences between the patients treated with or without hyperthermia, either with regard to the survival ($p = 0.1893$) or the rate of local control ($p = 0.58$). The survival was significantly worse among the patients with Stage IIb disease who received hyperthermia ($p = 0.0162$) although there was no difference in their rate of local control ($p = 0.7988$). Further analysis is necessary to determine if the difference in survival is due to a greater incidence of distant metastases or some other cause. Acute Grade 2–3 toxicity was seen in 10/55 patients (18%) treated by hyperthermia and in 2/55 of the patients (4%) treated without hyperthermia ($p = 0.01$). There was no significant difference in the late toxicity observed in the two arms.

Conclusion: This prospective randomized study failed to show any benefit from the addition of hyperthermia to radiotherapy in the treatment of locally advanced carcinoma of the uterine cervix. The acute toxicity was significantly greater among the patients receiving hyperthermia, and the survival was significantly worse among the Stage IIb patients receiving hyperthermia even though there was no difference in the local control rate.

Uterine cervical cancer, Hyperthermia, Radiotherapy, Combined modality, Randomized clinical trial.

Reprint requests to: Masahiro Hiraoka, M.D., Department of Therapeutic Radiology and Oncology, Kyoto University Graduate School of Medicine, 54 Shogoin Kawaharacho, Sakyo-ku, Kyoto, 606-8507, Japan. Tel: (+81)75-751-3417; Fax: (+81)75-771-9749; E-mail: hiraok@kuhp.kyoto-u.ac.jp

This study is supported by a grant of the International Atomic Energy Agency.

Received Sep 24, 2003, and in revised form Mar 29, 2004. Accepted for publication Apr 20, 2004.

INTRODUCTION

It is well known that hyperthermia above 42°C is cytotoxic itself, and the effect is increased under low pH or low nutritional conditions which are likely to occur in tumor tissues. Hyperthermia can be used to enhance the effects of radiation. Also, cells in the DNA synthetic phase of the cell cycle are relatively resistant to radiations, but particularly sensitive to hyperthermia. Thus, a combined treatment may, in some circumstances, be an advantage (1–3). In addition to the above-mentioned cellular effects, hyperthermia is likely to cause more damage to microvasculature of tumors than those of normal tissues. This vascular damage may lead to selective destruction of tumors, and the resulting decrease in blood flow of tumors would allow them to attain higher temperatures during the following hyperthermia (4).

Major efforts have been devoted to the development of deep-heating equipment. The most commonly used deep-heating method is regional heating. Because regional heating techniques apply energy to the deep-seated tumors in an unfocused manner, energy is also delivered to the adjacent normal tissues. Under such conditions, selective heating of tumors over the normal tissue is possible only when heat escape is more predominant in the normal tissue. An annular phased-array system delivering 60–80 MHz electromagnetic waves (5) and a radiofrequency (RF) capacitive heating apparatus (6) are two major regional heating devices available. The former system has the advantage in that subcutaneous fat is not excessively heated, and it is thus suitable for obese patients. However, this method causes systemic symptoms such as tachycardia and malaise which result from the use of large-sized applicators.

In RF capacitive heating, the size of the electrodes to be used is determined according to the size and location of the tumor. When the tumor is eccentricity located, a pair of different-sized electrodes is employed with the smaller one being placed on the skin close to the tumor so that the high temperature area is shifted toward the lesion. The advantages of RF capacitive heating are its wide applicability to various anatomic sites (7, 8) and relatively small systemic stress. The disadvantage is the excessive heating of subcutaneous fat, and it is shown that a patient with the subcutaneous fat of more than 2 cm in thickness is difficult to be heated with this heating modality.

Several prospective randomized trials for superficial tumors, including malignant melanoma, breast cancer, and neck node metastasis, have demonstrated significant improvement in the local response rate with the use of hyperthermia (9–11). The only exception is a trial carried out by the Radiation Therapy Oncology Group in the United States. The trial failed to show a difference in the response rate between radiation alone and radiation plus heat when the tumors treated were analyzed all together. The quality assurance and quality control have not been well-maintained, which might explain the negative results (12).

With regard to deep-seated tumors, four Phase III randomized trials have been reported. The first one is a trial which compared thermochemoradiotherapy with chemoradiotherapy as a preoperative treatment for esophageal cancers (13). The second is a trial for malignant gliomas where interstitial irradiation was compared with interstitial irradiation plus interstitial hyperthermia (14). Recently, two trials have been undertaken for tumors in the pelvis; one is for pelvic tumors (15, 16), and the other is for uterine cervical cancers (17). Radiotherapy plus hyperthermia was compared with radiotherapy alone in all of those trials, and improvement of both local response rate and survival outcome has been demonstrated.

The incidence of uterine cervical cancers is especially high in developing countries. The control of locally advanced pelvic tumors is difficult with conventional treatment modalities. This imposes a serious problem on developing countries where those malignancies are often detected at advanced stages. Since the two trials for the uterine cervical cancers have been undertaken in a single developed country, an internationally coordinated multicenter trial including developing countries was considered worthwhile, as improved treatment of locally advanced tumors would have an important impact on quality of life and longevity. Based upon the several biologic rationales and in view of the recent advances in heating and thermometry techniques, radiotherapy in combination with hyperthermia was investigated by a multi-institutional prospective randomized trial sponsored by the International Atomic Energy Agency (IAEA). The primary purpose was to clarify whether the combination of hyperthermia and radiotherapy improved the rate of local control, compared with radiotherapy alone.

METHODS AND MATERIALS

Between October 1998 and May 2002, 110 patients, in the age group of 20–75 years, with biopsy-proven carcinoma of the uterine

Table 1. Patient accrual

Location	Institution	RT alone	RT and HT	Total
Chennai, India	Cancer Institute	27	27	54
Kiev, Ukraine	Kiev City Oncology Centre	14	14	28
Pusan, Republic of Korea	Mary Knoll Hospital	9	9	18
Gangzhou, China	Sun Yat-sen Univ. of Medical Sciences	4	5	9
Beijing, China	China-Japan Friendship Hospital	1	0	1
Total		55	55	

Abbreviations: HT = hyperthermia; RT = radiation therapy.

Table 2. Treatment methods

Location	Brachytherapy	RT dose to Point A (Gy)*	No. HT sessions*	Duration of HT session (min)*	No. temperature measurements*	Tave*
Chennai, India	LDR	67.8 (2.0–72.5)	4.9 (0–7)	60 (59–60)	2.8 (2–5)	41.8 (41.3–42.5)
Kiev, Ukraine	HDR	63.5 (14.0–68.0)	6.2 (5–7)	58.3 (53.6–60)	2.4 (0–6)	42.0 (40.1–44.4)
Pusan, Republic of Korea	HDR	82.5 (54.0–92.3)	4.6 (3–6)	60.4 (60–61.7)	2.8 (1–6)	38.1 (37.5–39.0)
Gangzhou, China	HDR	86.1 (78.0–96.0)	5.8 (4–7)	55.5 (50.8–60.4)	1.8 (0–3)	40.4 (40.2–40.6)
Beijing, China	HDR	46.0 (46.0–46.0)	N/A	N/A	N/A	N/A
Total						

Abbreviations: LDR = low dose rate; HDR = high dose rate; RT = radiation therapy; HT = hyperthermia; N/A = not applicable; Tave = average tumor temperature.
* Mean (range)

cervix, in International Federation of Gynecology and Obstetrics (FIGO) Stages IIB, III, or IVA, were registered and randomized to treatment by radiotherapy with (n = 55) or without (n = 55) hyperthermia (Table 1). The study was approved by each institution's ethical committee. The eligibility criteria included life expectancy at least 3 months, World Health Organization performance score 0–2, and ability to give informed consent according to institutional ethical committee guidelines. Patients were not considered eligible if they had a pacemaker or other large metal objects within the treatment area, any prior radiotherapy to the treatment area, distant metastases, subcutaneous fat thickness more than 3 cm (for RF capacitive heating), pregnancy, or another cancer within the past 5 years.

The patients were stratified by institution, stage, and histologic type. After randomization, each patient was planned to receive external beam radiation therapy and brachytherapy. For the patients randomized to receive hyperthermia, a minimum of five sessions (60 min each, once per week) were planned, employing RF capacitive heating. Intratumoral temperature was planned to be measured at the first hyperthermic treatment, and at least once more during the course of treatment.

Of the 110 patients, 110 actually received external beam radiotherapy, and 96 received brachytherapy also. Of the 55 patients randomized to receive hyperthermia, 49 received at least one session of hyperthermia. Forty-seven of those 49 patients had temperature measurement at least twice; as required according to the protocol.

The details of external beam radiotherapy, brachytherapy, hyperthermia, and thermometry at each of the participating institutes are as follows (Table 2).

Chennai

The patients were treated with 6-MV X-rays using 4-field box technique delivering a minimum tumor dose of 200 cGy/fraction, 5 fractions/week, to a total dose of 50 Gy in 5 weeks to the whole pelvis. Then a single low-dose-rate intracavitary application was performed delivering a further dose of 20–22 Gy to Point A by remote afterloading technique. Only in 2 patients intracavitary application was not possible and external beam radiotherapy was continued to a further dose of 20 Gy.

The patients who had intracavitary application were also given supplementary parametrial irradiation with 6-MV X-rays using two opposing fields with central shielding so that the lateral pelvic dose was raised to 65–70 Gy. Hyperthermia was delivered using Thermotron RF-8, a capacitive type of unit generating RF radiation at a frequency of 8 MHz. It was delivered immediately after radiotherapy, once a week, on Tuesdays. A pair of same-sized surface electrodes along with intracavitary thermal applicator inserted into the posterior vaginal fornix was used. The size of the surface electrodes was larger than the thickness of the body. Minimum tumor temperature of more than 41°C was attempted, and it was maintained for 1 h. Blood pressure and pulse rate were checked before and after the treatment. Drugs that might affect the level of consciousness were not used. Tumor temperatures were measured at least twice during the course of the treatment. The first measurement was done at the time of the first hyperthermic treatment. One of the thermocouples was taped to the intracavitary thermal applicator with a ball of wet cotton in between so that there was a separation of at least 1 cm in between them. Other thermocouples were placed in the vaginal fornices. Starting after

Table 3. Patient characteristics

		RT alone (n = 55)	RT and HT (n = 55)
Age*		50.0 (22–71)	45.0 (27–72)
Performance status	0	19	18
	1	36	36
	unknown	0	1
Hemoglobin (g/dL)*		11.5 (9.0–15.3)	11 (6.7–14.3)
Prior treatment	None	54	52
	Surgery	0	2
	Chemotherapy	1	0
	Unknown	0	1

Abbreviations: HT = hyperthermia; RT = radiation therapy.
* Median (range)

Table 4. Tumor characteristics

		RT alone (n = 55)	RT and HT (n = 55)	
FIGO stage	II b	29	27	
	III a	6	3	
	III b	19	23	
	IV a	1	2	
Histologic type	Squamous	52	51	
	Adeno	1	3	
	Others	2	1	
Histologic grade	GX	11	11	
	G1	4	7	
	G2	9	6	
	G3	31	31	
Tumor size (cm^3)*†		49.5 (8.0–185.2)	60.3 (14.8–339.3)	p = 0.09

Abbreviations as in Table 3
* X × Y × Z × π/6
† Median (range)

the eleventh patient (following the site visit by the corresponding author), one of the thermocouples was inserted into the cervical canal. The temperature measured in the cervical canal was, as expected, lower than that measured without inserting the thermocouple in the cervical canal. The mean temperature in the cervical canal was 40°C (range, 37.9–42.7°C), whereas otherwise the mean maximum temperature was 42.6°C (range, 41.4–44.4°C) and the mean minimum temperature was 41.1°C (range, 41–41.7). Body temperature (temperature in the rectum) was also monitored during the treatment. The mean was 40.5°C (range, 38.1–42.5°C).

Pusan

External beam radiation therapy was given to the whole pelvis by 10-MV photon beam, with 4-field box technique, delivering daily 180–200 cGy, five times per week, to a total dose of 5040 cGy. Then parametrial boost radiation was given, with bladder and rectal shield, delivering 540 cGy in 3 fractions. The boost treatments were given 2 times per week during intracavitary brachytherapy for shortening overall treatment duration. The total dose delivered was 6800–9187 cGy (including boost dose to Point B and intracavitary irradiation). One patient received intracavitary irradiation with vaginal mold (7 fractions). A Co-60 Ralstron machine (Shimatzu, Japan) was used for intracavitary irradiation. 300 cGy/fraction were given at point A, 3 times per week, and the number of fractions ranged from 7 to 13 (mean, 11.53). Hyperthermia was given before radiation therapy, for 60 min/session once a week, with an 8-MHz RF capacitive type heating machine; and the number of sessions was 3–6 (mean, 4.56). Intratumoral temperature was measured 1–6 times (mean, 2.78). Body temperature and pulse rate were also noted before and after hyperthermia.

Hyperthermia-related parameters were as follows: hyperthermia (HT) time: 60–62 min (mean, 60.3 min); maximum power: 450–608 Watt (mean, 520 W); maximum tumor temperature (Tmax): 37.7–39.9°C (mean, 38.5°C); minimum tumor temperature (Tmin): 36.4–37.9°C (mean, 37.2°C); average tumor temperature (Tave): 37.5–39.0°C (mean, 38.1°C).

Kiev

External beam radiotherapy was given to the whole pelvis, with a Telecobalt unit, using a pair of parallel opposed fields, delivering a dose of 200 cGy per fraction, to a total dose of 14–18 Gy, followed by irradiation of the pelvic side walls, with central shield, delivering a further dose of 24–32 Gy. High-dose-rate (HDR) intracavitary therapy was done delivering 50 Gy in 10 fractions.

Hyperthermia was given after radiotherapy. The heating was maintained for 50–60 min, and the temperature attained was in the range of 39.5–44.8 °C.

Table 5. Treatment parameters for radiation therapy

	RT alone (n = 55)	RT and HT (n = 55)	p Value
External beam dose to Point A (Gy)*	50 (2–70)	50 (14–70)	0.44
Data missing	4	5	
Brachytherapy dose to Point A (Gy)*	22 (0–68)	22 (0–66)	0.74
Data missing	4	5	
Total dose to Point A (Gy)*	84 (2–96)	84 (64–96)	0.19
Data missing	4	5	
External beam dose to pelvic wall (Gy)*	60 (2–74)	61 (40–70)	0.24
Data missing	4	5	
Overall treatment time (days)*	51 (33–108)	52 (33–92)	0.96
Data missing	5	5	

Abbreviations: HT = hyperthermia; RT = radiation therapy.
* Median (range)

Table 6. Treatment parameters of hyperthermia for patients randomized to receive hyperthermia

	RT and HT (n = 55)
Total number of hyperthermia sessions*	5 (0–10)
Data missing	4
Number of sessions with thermometry/patient*	2 (0–6)
Data missing	6
Average of Tmax*	42.1 (37.7–46.6)
Data missing	7
Average of Tmin*	41 (36.4–43.8)
Data missing	7
Average of Tave*	41.6 (37.4–44.4)
Data missing	7

Abbreviations: HT = hyperthermia; RT = radiation therapy.
* Median (range)

Gangzhou

All patients were treated with photons of energy 6–18 MV or ^{60}Co, delivering 2 Gy/fraction, 5 fractions/week, using parallel opposed AP-PA portals or 4-field box technique. 30 Gy was delivered to the whole pelvis and then a further 20 Gy to the pelvic wall with a midline shield. Brachytherapy was performed with HDR irradiation technique, delivering a dose of 48–60 Gy to Point A, with a frequency of once a week to a total of 8–10 fractions. Brachytherapy was delivered concomitantly with teletherapy. Hyperthermia was delivered within 30 min of radiotherapy, once a week, to a total of 4–6 sessions. A pair of electrodes 25–30 cm in diameter was used. Overlay bolus was applied for cooling the skin and subcutaneous layer with cooling water to a temperature of 10–15 °C. Minimum tumor temperature of more than 41°C was attempted, and it was maintained for 1 h. Body temperature, blood pressure, and pulse rate were measured before and after every hyperthermia session. Intratumoral temperatures were measured at least once during the course of the hyperthermic treatment. The first measurement was done at the first treatment. The thermal probe was inserted into the tumor directly. Multipoint thermal probes were used; the minimum depth of the probe was 3 cm.

Beijing

External beam radiotherapy was given using photons from a linear accelerator with 4-field box technique, delivering a dose of 2 Gy/fraction to a total dose of 30 Gy. HDR brachytherapy was carried out, delivering 6 Gy/fraction, 2 fractions/week, to a total dose of 24 Gy.

Quality assurance

The equipment and the policies and procedures at each participating institution (except Pusan) were personally inspected at least once by the corresponding author, to ensure that quality assurance procedures were in place and were followed for treatment according to the protocol guidelines.

Posttreatment evaluation

All patients were followed up regularly by physical examination and, when appropriate, by diagnostic imaging such as computed tomography/magnetic resonance imaging scans. The evaluation was performed every 3 months for the first 6 months, then at 12 months, followed by at least once every year.

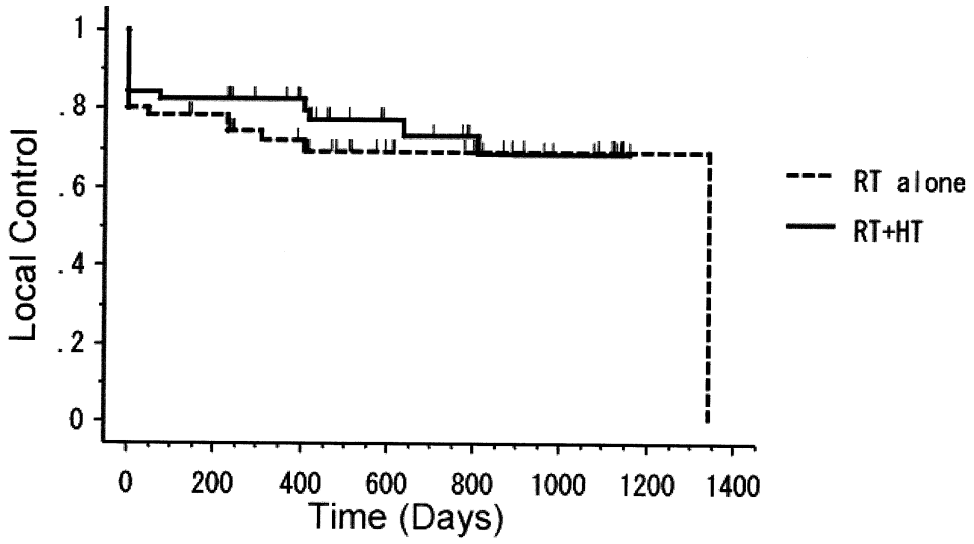

Fig. 1. The proportion of the patients alive (Kaplan-Meier method) analyzed according to the treatment arm (p = 0.1893).

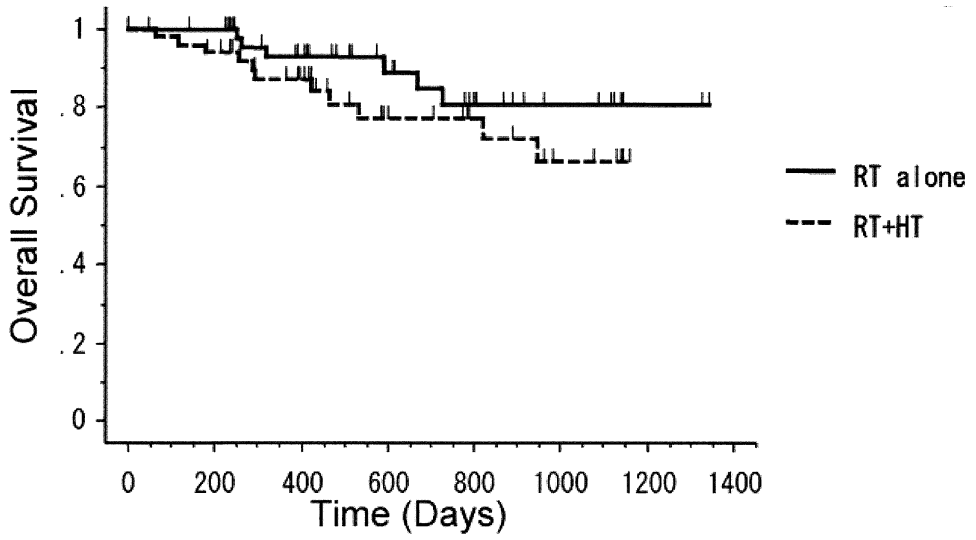

Fig. 2. The proportion of the patients with local control (Kaplan-Meier method) analyzed according to the treatment arm ($p = 0.58$).

Statistical design

The principal end-point was local control. It was assumed that with radiotherapy alone the local control rate was 60%, and in order to detect an improvement of 20% by adding hyperthermia, 129 patients would be required in each arm. However, the study was terminated after 110 patients had been randomized because the preliminary analysis showed lack of any benefit from hyperthermia and the slow rate of accrual made it unrealistic to enroll the originally planned number of patients.

RESULTS

As shown in Tables 3 and 4, the two arms were well balanced with regard to the patient factors and tumor factors. As shown in Table 5, the radiotherapy factors were also well balanced between the two arms. Table 6 shows the treatment parameters of hyperthermia for the patients randomized to receive hyperthermia.

The median follow-up period was 466 months for all the patients and 512 months for the surviving patients. Seventeen of the 110 patients are known to have died at this writing, 16 due to the cervical cancer and one due to some other cause. The observed survival rates of the patients (intent-to-treat analysis) are shown in Fig. 1 and the rates of local control in Fig. 2. There were no significant differences between the patients treated with or without hyperthermia.

Figures 3, 4, and 5 show the local control rates analyzed according to the stratification variables, viz. the institution, the stage of the disease, and the histologic subtype. The local control of the patients from institution X was significantly lower than the others. There was no significant difference in the rates of local control according to the stage of the disease.

The survival was significantly worse among the patients with Stage IIb disease who received hyperthermia ($p = 0.0162$), although there was no difference in their rate of local control ($p = 0.7988$) (Figs. 6 and 7). Further analysis is necessary to determine if the difference in survival is due

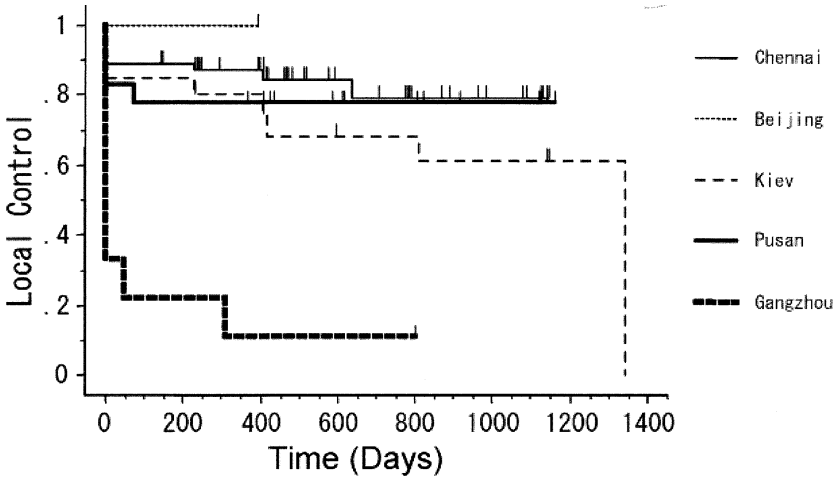

Fig. 3. The proportion of the patients with local control, analyzed according to institution ($p \leq 0.0001$).

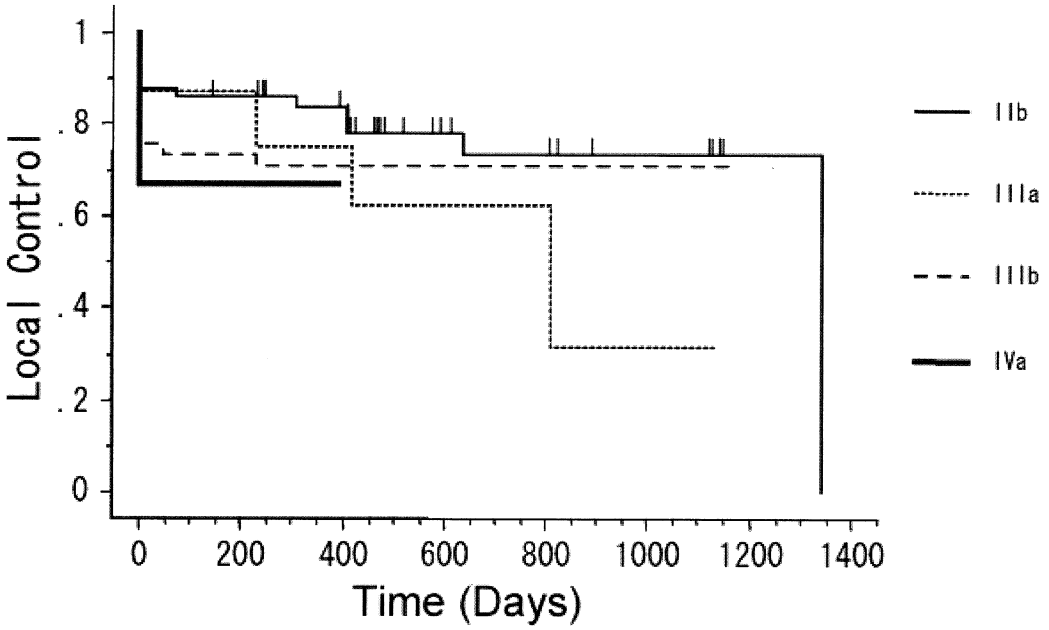

Fig. 4. The proportion of the patients with local control, analyzed according to the stage of the cancer ($p = 0.4995$).

to a greater incidence of distant metastases or some other cause.

Acute and late toxicity

No Grade 4 acute toxicity was seen. Acute Grade 3 toxicity was seen in only 1 patient treated by hyperthermia and in none of the patients treated without hyperthermia. Grade 2 toxicity was seen in 9 of 55 patients (17%) treated by hyperthermia and 2 of 55 patients (4%) treated by radiotherapy alone. The kinds of acute Grade 2–3 toxicities observed and late toxicity are shown in Table 7. There was no significant difference in the late toxicity observed between the two arms.

DISCUSSION

Based upon the several biologic rationales and in view of the recent advances in heating and thermometry techniques, radiotherapy in combination with hyperthermia was investigated by a multi-institutional, prospective, randomized trial sponsored by the IAEA, to clarify whether the combi-

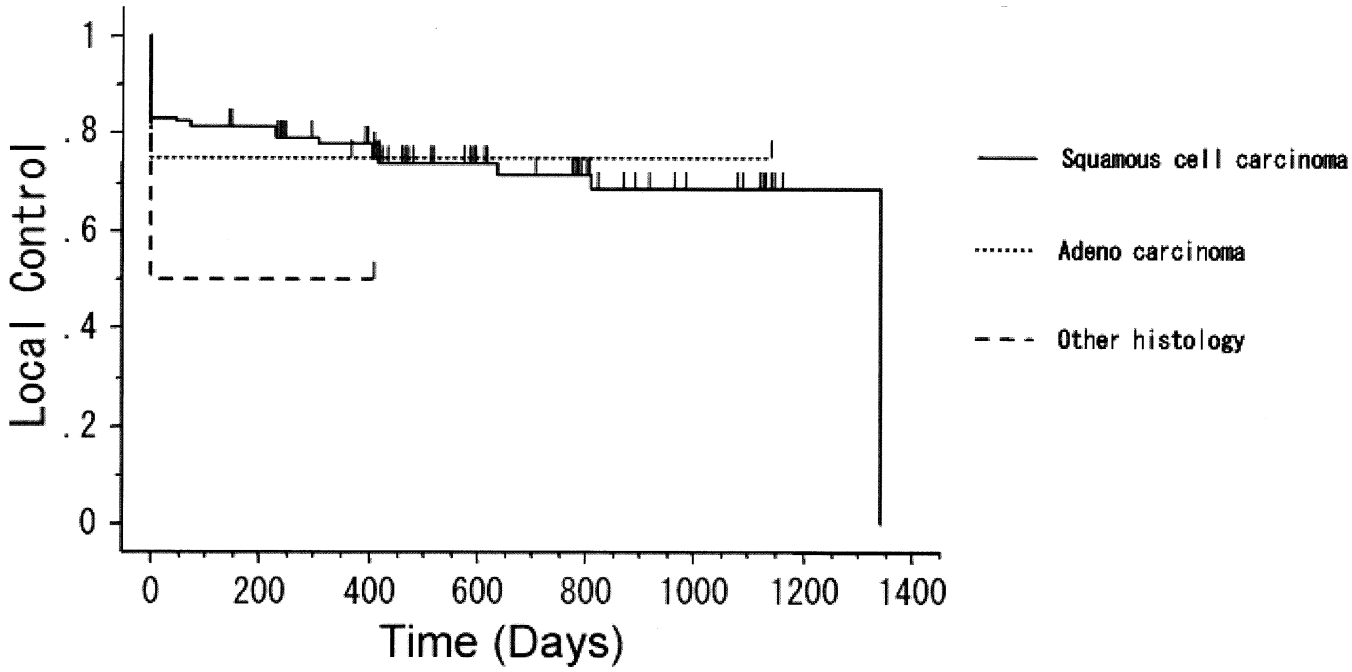

Fig. 5. The proportion of the patients with local control, analyzed according to the histologic type ($p = 0.6450$).

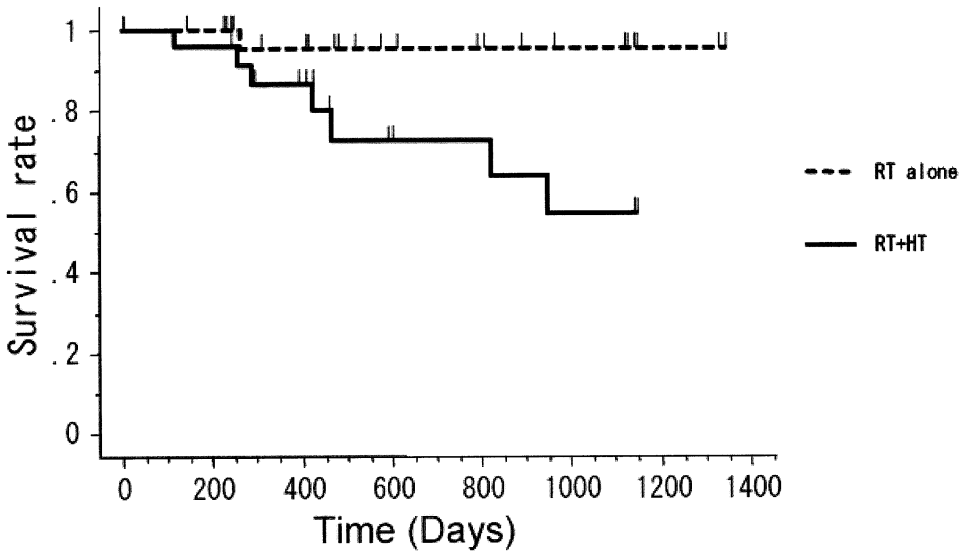

Fig. 6. The proportion of the patients with Stage IIb disease alive, analyzed according to the treatment received (p = 0.0162).

nation of hyperthermia and radiotherapy improves the rate of local control, compared with radiotherapy alone, in patients with biopsy-proven locally advanced carcinoma of the uterine cervix. A total of 110 patients were registered and randomized to treatment by radiotherapy with (n = 55) or without (n = 55) hyperthermia. They were treated in accordance with the common protocol agreed by the participating institutions, and the follow-up data were computed and analyzed. In this study, there were no significant differences between the patients treated with or without hyperthermia in both the local control rate as well as the survival rate. These results are different from the previous two reports (16, 17) which showed a significant improvement in both local control rate and survival for uterine cervical cancers by the addition of hyperthermia. The present trial was carried out in patients with locally advanced cervical cancer alone, and the patients were from the developing countries. The failure of the present study to show enhanced local control and survival rates may be partly because the tumor volumes had been too large for any therapeutic benefit due to the addition of hyperthermia. It should also be kept in mind that the median tumor volume

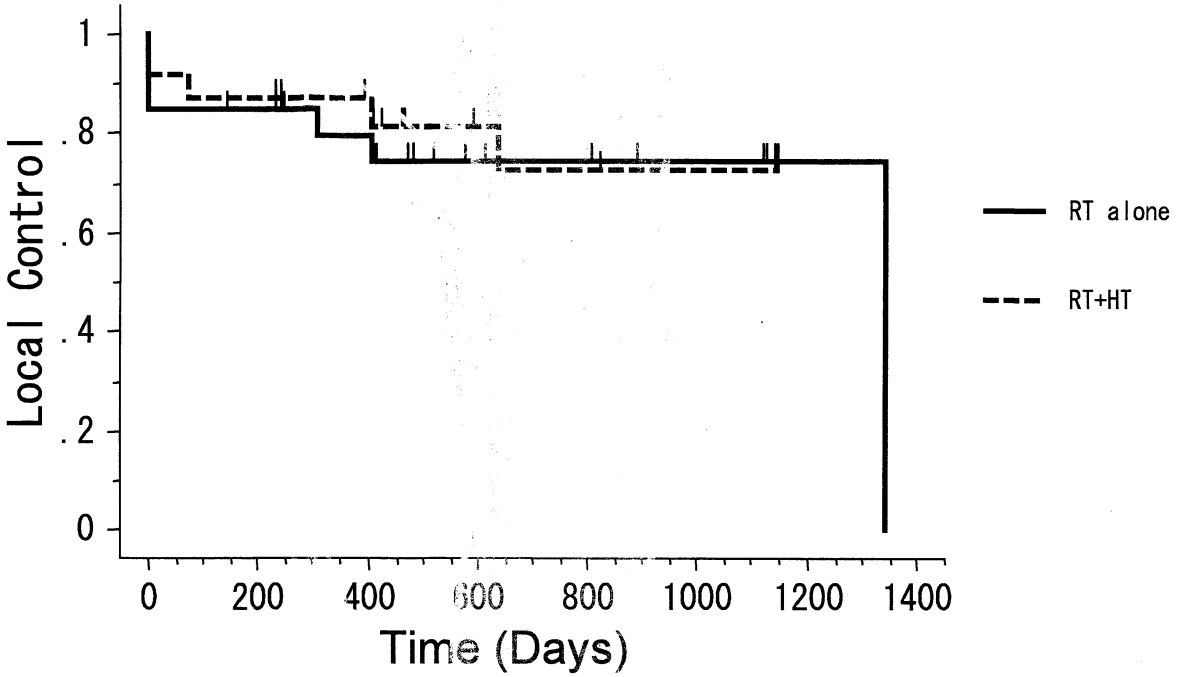

Fig. 7. The proportion of the patients with Stage IIb disease with local control, analyzed according to the treatment received (p = 0.7988).

Table 7. Acute and late toxicity

		RT alone (n = 55)	RT and HT (n = 55)
Acute toxicity			
	Grade II	2 proctitis	2 fatnec* + 4 proctitis + 3 colitis
	Grade III	0	1 blister
	Grade IV	0	0
Late toxicity			
	Grade II	1 bladder + 2 bowel	2 bowel
	Grade III	2 bowel	2 bowel
	Grade IV	1 bowel	0

Abbreviations as in Table 6
* Fat necrosis.

in the study arm was 60.3 cc whereas in the control arm it was 49.5 cc.

When the local control rates were analyzed according to the stratification variables, viz. the institution, the stage of the disease, and the histologic subtype, there was no significant difference in the rates of local control according to the stage of the disease and the histologic subtype. The local control of the patients from institution X was significantly lower than the others.

The survival was significantly worse among the patients with Stage IIb disease who received hyperthermia ($p = 0.0162$), although there was no difference in their rate of local control ($p = 0.7988$). Further analysis is necessary to determine if the difference in survival is due to a greater incidence of distant metastases or some other cause.

In this study, addition of hyperthermia resulted in more of acute toxicity (18.2% vs. 3.6%) but there was no significant difference in the late toxicity observed between the two arms.

In summary, this prospective randomized study failed to show any benefit from the addition of hyperthermia to radiotherapy for the treatment of locally advanced carcinoma of the uterine cervix. The acute toxicity was greater among the patients receiving hyperthermia and the survival was significantly worse among the Stage IIb patients receiving hyperthermia even though there was no difference in their local control rate.

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