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Report of a study using phantom materials, and clinical experience with simultaneous radio-hyperthermotherapy.

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Abstract

Simultaneous radiohyperthermotherapy (SRH) is a combined hyperthermia-radiation therapy in which irradiation is given during heating. Mutual interference between the high energy radiotherapy system (Toshiba LMR-15A) and the 13.56 MHz capacitive heating system (Omron HEH-500C) was tested with phantom materials prior to a clinical trial with SRH. The energy and flatness of irradiation were not affected by the heating system within the range of clinical use. The high energy radiotherapy system did not affect the increase or distribution of temperature during simultaneous treatment. The results of this phantom study indicated that these apparatuses would not produce clinically significant mutual interference during SRH. A clinical trial was performed on a 57-year-old woman with postoperative recurrence of rectal cancer. This is the first reported clinical case treated with true SRH in which external irradiation was administered during mid capacitive heating. Twelve SRH treatments were performed on the recurrent lesion at a frequency of twice a week for six weeks using the apparatuses described above. There was a significant reduction in pain after treatment. The tumor marker carcinoembryonic antigen (CEA) level decreased after treatment. On CT images taken after treatment, the tumor site became a low density area which indicated necrosis. There were no side effects. These results suggest that further clinical study of SRH should be performed to clarify its advantages.

KEYWORDS: hyperthermia, capacitive heating, radiotherapy, phantom study, simultaneous radio-hyperthermotherapy

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Report of a Study Using Phantom Materials, and Clinical Experience with Simultaneous Radio-Hyperthermotherapy

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Simultaneous radiohyperthermotherapy (SRH) is a combined hyperthermia-radiation therapy in which irradiation is given during heating. Mutual interference between the high energy radiotherapy system (Toshiba LMR-15A) and the 13.56 MHz capacitive heating system (Omron HEH-500C) was tested with phantom materials prior to a clinical trial with SRH. The energy and flatness of irradiation were not affected by the heating system within the range of clinical use. The high energy radiotherapy system did not affect the increase or distribution of temperature during simultaneous treatment. The results of this phantom study indicated that these apparatuses would not produce clinically significant mutual interference during SRH. A clinical trial was performed on a 57-year-old woman with postoperative recurrence of rectal cancer. This is the first reported clinical case treated with true SRH in which external irradiation was administered during mid capacitive heating. Twelve SRH treatments were performed on the recurrent lesion at a frequency of twice a week for six weeks using the apparatuses described above. There was a significant reduction in pain after treatment. The tumor marker carcinoembryonic antigen (CEA) level decreased after treatment. On CT images taken after treatment, the tumor site became a low density area which indicated necrosis. There were no side effects. These results suggest that further clinical study of SRH should be performed to clarify its advantages.

Key words : hyperthermia, capacitive heating, radiotherapy, phantom study, simultaneous radio-hyperthermotherapy

Combined radiotherapy and hyperthermotherapy gives consistent clinical results in the treatment of cancer lesions. In the present clinical treatment, hyperthermotherapy should follow radiotherapy as soon as possible and sequential

radio-hyperthermotherapy is now a standard procedure. However, basic *in vitro* and *in vivo* studies show that during simultaneous irradiation and heating, the heating will increase radiosensitivity markedly (1-4). Thus, we expect that clinical application of simultaneous radio-hyperthermotherapy (SRH) will enhance the effec-

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tiveness of tumor treatment.

No reports on clinical application of SRH have been published in Japan. Some investigators reported a combination of interstitial brachytherapy and hyperthermia by SRH (5). A few reports also referred to hyperthermia induced immediately after external irradiation as SRH (6-10). In July 1991 we started to apply true SRH clinically using capacitive heating and simultaneous external irradiation. Before clinical application we used phantoms to investigate the occurrence of interferences during the simultaneous operation of capacitive heating and external irradiation devices. This report includes details of a clinical trial case.

Materials and Methods

The irradiation device used was a Toshiba LMR-15A and the 13.56 MHz capacitive heating device was an Omron HEH-500C. We examined the occurrence of interferences during the simultaneous operation of both devices observing the following items.

Examination of changes in radiation energy and flatness during the simultaneous operation of a capacitive heating device. We assumed that the energy of X-rays would not change unless there was a change in electron beam energy and thus used electron beams to observe changes in radiation energy. We placed a Kodak X-O mat TL film and the electrodes of the capacitive heating device with a diameter of 10 cm into a physiologic saline solution phantom. An area of $10 \times 10 \text{ cm}^2$ of this solution was irradiated parallel to the film from above with a source surface distance (SSD) of 97 cm using an electron beam of 10 MeV or 14 MeV. We heated this construction simultaneously from its sides with an output between 0 and 400 W. We then developed this film in a Konica QX-1200 developer and continuously measured density along the central axis of the beam with a Konica made PDS-15. Using the dose-density curve we converted density into dose and prepared a percentage depth dose curve. We then calculated the mean electron energy at surface from this depth of 50 % dose (R_{50}) and examined whether heating changed this energy.

To ascertain changes in flatness of the radiation we used the same method to measure a plane 3 cm below the water surface vertical to the beam axis using a 14 MeV electron beam. The results were converted to radiation

dose and examined. Flatness due to SRH of a transit 10 MV X-ray beam from the physiologic saline solution phantom was observed using a Victoreen made Mode 7000 therapy beam evaluation system.

Investigation of changes in heating and temperature distribution during the simultaneous operation of an external irradiation and a capacitive heating device. We irradiated an area of $10 \times 10 \text{ cm}^2$ of a physiologic saline solution phantom containing a thermocouple thermometer and the electrodes of the heating device with a diameter of 10 cm from above with both an electron beam of 10 MeV and X-rays of 10 MV from an SSD of 97 cm to observe changes in temperature rise. Simultaneously we observed in intervals of 15 sec whether irradiation caused changes in temperature, while this structure was heated for 5 min with an output of 500 W.

To observe fluctuations in temperature distribution, a liquid crystal thermosensor (Japan Capsular Products) was inserted into a standard muscle tissue equivalent agar phantom. We placed electrodes with a diameter of 15 cm on the sides and heated an arrangement for 55 min with an output of 200 W. Later we examined the occurrence of changes in temperature distribution due to simultaneous irradiation from above of an area of $5 \times 5 \text{ cm}^2$ from an SSD of 88 cm at a dose rate of 100 cGy/min for 5 min with a 10 MV X-ray beam.

Results

Influence of the simultaneous operation of a capacitive heating device on radiation energy and flatness. Fig. 1 shows the changes in the percentage depth dose curve due to operation of a heating device for a physiologic saline solution phantom using 10 or 14 MeV electron beams. Table 1 shows the depth of 50 % dose (R_{50}), the mean electron energy at surface, and the depth of 80 % dose (R_{80})(11) obtained from this curve. During heating with 400 W, R_{80} values increased by 0.5 mm for an electron beam of 10 MeV, and by 1.5 mm for 14 MeV, but these differences are not clinically significant.

Fig. 2 shows the changes in flatness of a 14 MeV electron beam in a physiologic saline solution phantom due to the operation of a heating device. During the simultaneous operation the

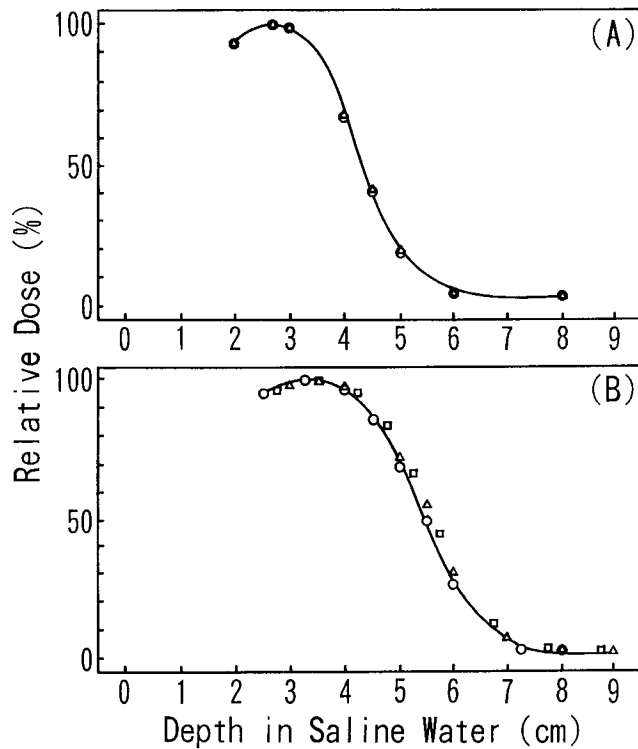


Fig. 1 Electron energy changes by capacitive heating. (A) Percentage depth dose curve of the 10 MeV electron. \circ , Output 0 W; \triangle , Output 400 W. (B) Percentage depth dose curve of the 14 MeV electron. \circ , Output 0 W; \triangle , Output 200 W; \square , Output 400 W. The depth of 50% dose (R_{50}), the mean electron energy at surface and the depth of 80% dose (R_{80}) in Table 1 were obtained from this curve.

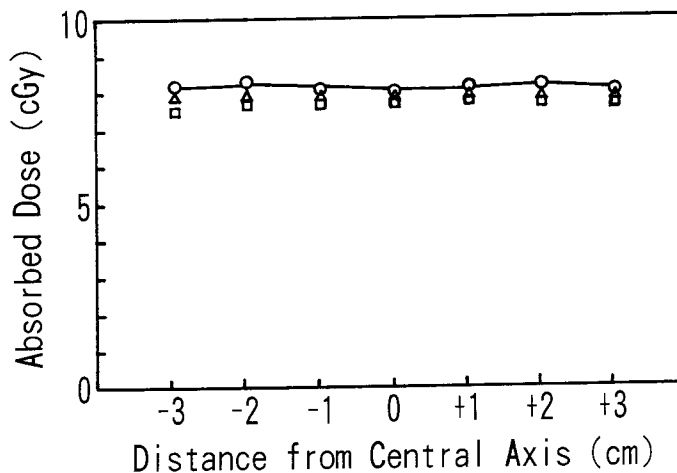


Fig. 2 Electron flatness changes by capacitive heating. \circ , Output 0 W; \triangle , Output 200 W; \square , Output 400 W. The changes in flatness within a distance of 3 cm on both sides of the central axis of the beam remained within 3% for an output of the heating device of up to 400 W during the simultaneous operation.

Table 1 Effect of capacitive heating on electron energy

	10 MeV electron		14 MeV electron		
	Output of capacitive heating (W)				
	0	400	0	200	400
Mean electron energy at surface (MeV)	10.0	10.1	12.8	13.2	13.3
R ₈₀ (cm)	3.70	3.75	4.70	4.75	4.85
R ₅₀ (cm)	4.30	4.35	5.45	5.60	5.65

R₈₀: the depth of 80 % dose; R₅₀: the depth of 50 % dose.

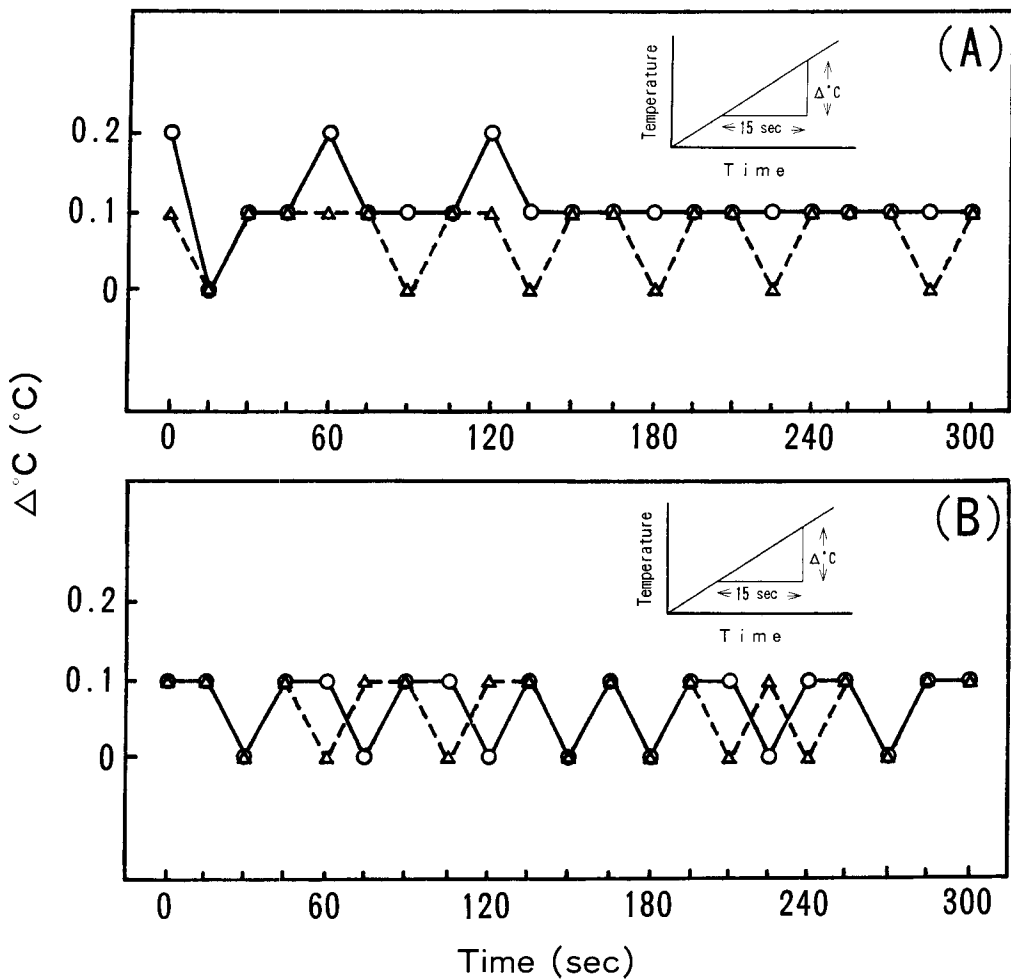


Fig. 3 Temperature increase changes by irradiation. (A) 14 MeV electron. \triangle , With electron beam; \circ , Without electron beam. (B) 10 MV X-ray. \triangle , With X-ray beam; \circ , Without X-ray beam. A comparison of heating alone and combined irradiation did not show any differences.

changes in flatness within a distance of 3 cm on both sides of the central axis of the beam remained within 3% for an output of the heating device of up to 400 W, which was regarded as insignificant. Additionally, we examined the changes in flatness of a 10 MV X-ray beam on the transit side of a physiologic saline solution phantom during the simultaneous operation with a Victoreen made Mode 7000 therapy beam evaluation system, but could not find any changes due to the operation of the heating device.

Influence of an external irradiation device during the simultaneous capacitive heating on temperature rise and distribution. Fig. 3 shows the temperature rise in the phantom in intervals of 15 sec. A comparison of heating alone and combined irradiation did not show any differences. Fig. 4 shows the temperature distribution in a standard muscle tissue equivalent agar phantom measured with a liquid crystal thermosensor during a simultaneous treatment. Temperature distribution in vertical and horizontal directions was symmetric, similar to that of heating alone

and irrelevant to radiation dose distribution.

Case representation. The patient was a 57-year-old woman with local recurrences of a rectal cancer 2 years and 9 months after resection. Cancer tissue obtained at resection was identified as moderately differentiated adenocarcinoma. Fig. 5 shows the recurrent tumor localized at the original resection site ventral to the sacrum and dorsal to the vagina and uterus. It had invaded both the vagina and the sacrum. Radiotherapy was performed using a Toshiba LMR-15A with a 10 MV X-ray beam. The recurrent tumor was irradiated from all sides through 4 ports and three times every week (Tuesday, Wednesday and Friday) an area of $13 \times 19 \text{ cm}^2$ was irradiated through 2 anteroposteriorly opposing ports (Fig. 6A). Twice every week (Monday and Thursday) opposing left and right irradiation fields of $12 \times 18.5 \text{ cm}^2$ were treated with SRH (Fig. 6B). Radiation dose was 2 Gy per session at a dose rate of 200 cGy/min, a total of 60 Gy. We used the Omron made HEH-500C capacitive heating device with electrodes of 20 cm diameter attached

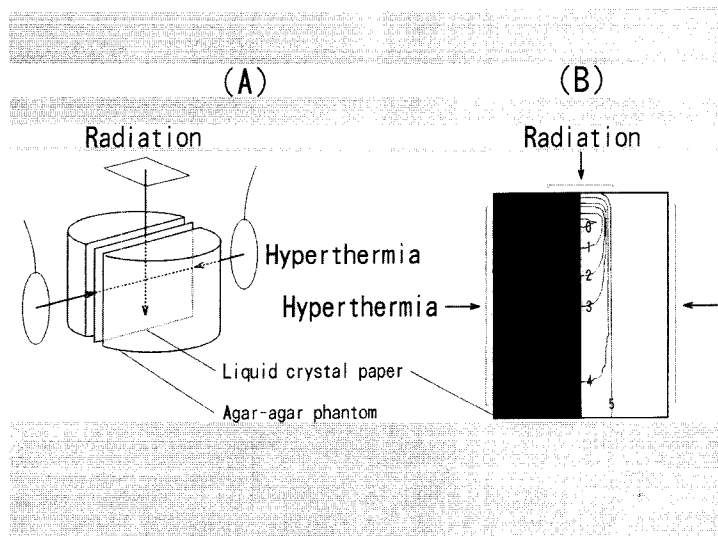


Fig. 4 Temperature distribution changes by irradiation. (A) Experimental schema. (B) Temperature distribution in SRH with 10 MV X-ray. The left side of the temperature distribution on liquid crystal thermosensor (left side) is symmetric in the vertical direction. There was no relation with the iso-dose curve (right side) of the X-ray beam calculated by Modulex (CMS Inc.). 0, 98%; 1, 90%; 2, 80%; 3, 70%; 4, 50%; 5, 30%.

anteroposteriorly for the heating. Hyperthermia was given twice a week (Monday and Thursday), 60 min each, for a total of 12 sessions. We inserted a thermocouple thermometer into the

bladder and tried to keep the temperature above 42°C. Thirty minutes after the initiation of the heating, irradiation was added to the heating. Average temperature during all 12 SRH sessions

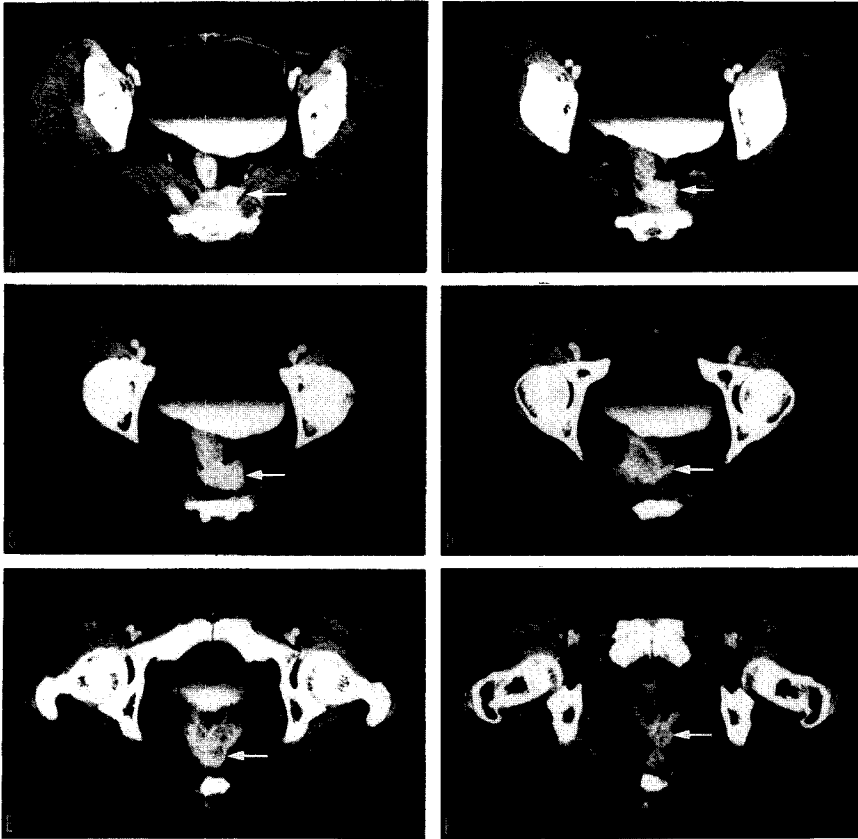


Fig. 5

Fig. 5 CT images before treatment. (A) to (F), Each image was taken at 1 cm intervals. The recurrent tumor was located at the original resection site ventral to the sacrum and dorsal to the vagina and uterus (arrows).

Fig. 6 Irradiation plan. (A) Irradiation simulation in the A-P direction. Irradiation alone was administered 3 times (Tue, Wed, and Fri.) a week. (B) Irradiation simulation in the R-L direction. Simulation was accomplished with electrodes. SRH was done twice (Mon. and Thu.) a week. Irradiation in the R-L direction was added to heat treatment in the A-P direction at mid heating. (C) CT images of the lesion before treatment. Arrow, the recurrent tumor. (D) Dose distribution calculated by Modulex (CMS Inc.). Irradiation was tailored to the lesion indicated at (C).

Fig. 7 Lesion changes on CT images. Arrows, the recurrent tumor. (A) Before treatment. (B) Immediately after treatment. (C) 1 month after treatment. (D) 3 months after treatment. Tumor size immediately after treatment was unchanged, but decreased about 20% 1 month after treatment. Its internal low density area increased more than 80%. This decrease of internal density was even more marked after 3 months.

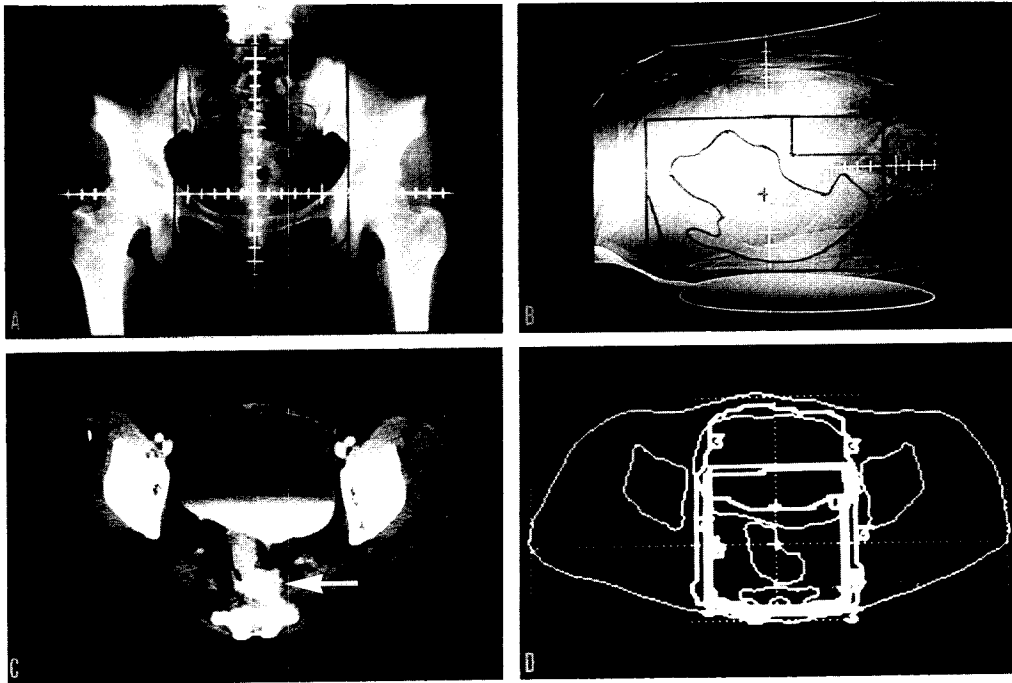


Fig. 6

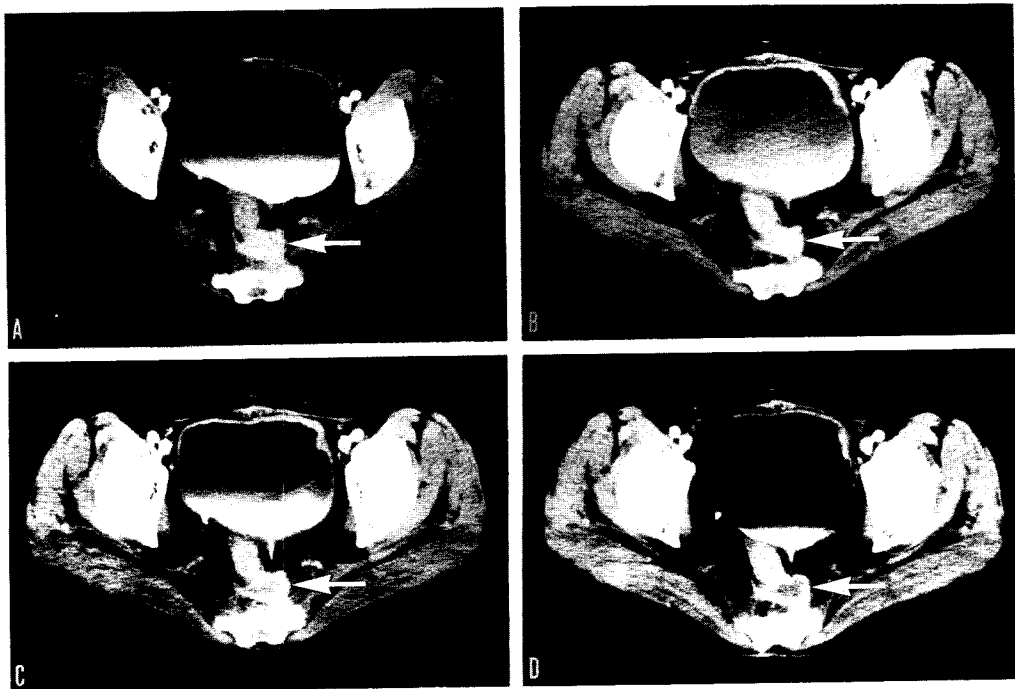


Fig. 7

was 41.1°C. For the duration of the treatment, patients received a chemotherapy regimen of daily 300mg of UFT (uracil plus tegafur in a molar ratio 1:4).

Fig. 7 shows enhanced computerized tomography (CT) images from before, immediately, 1 and 3 months after treatment. Tumor size immediately after therapy was unchanged (NC), but decreased about 20 % 1 month after the therapy. Its internal low density area increased more than 80 %. This decrease of internal density was even more marked after 3 months. Fig. 8 shows the changes in the concentration of the tumor marker carcinoembryonic antigen (CEA). Toward the end of the treatment it decreased markedly and fell to an even lower value 1 month after the therapy. The pain score of Radiation Therapy and Oncology Study Group (12) was 9 at the

start of the treatment, but fell to 2 immediately. One month after the treatment the score was 1. No serious side-effects occurred during the treatment.

Discussion

Basic *in vitro* studies regarding the time relation of combined radio- and hyperthermotherapy showed that enhancement of radiosensitivity due to heating was most marked in cells like RUC-2, CH-V79, CHO or KK-47 when irradiation and heating were performed simultaneously (1-3). Major causes of the thermal radiosensitization were suggested in molecular studies to be inhibition of DNA synthesis and or repair of DNA damage by hyperthermia (13). The enhancement effect of SRH is reported to be similar and marked in both *in vivo* and *in vitro* studies (4). The magnitude of this effect increased with increasing temperature (4, 14, 15) or heating duration (4, 14). Therapeutic gain factor (TGF) had been reported to increase during SRH in association with a temperature increase (15), while other reports stated it remained low (4). Some reports stated low values of the TGF for SRH compared with irradiation followed by hyperthermia (4), while other reports suggested the possibility of reaching high values (16). Since a low TGF is a problem for clinical applications of SRH, we designed the apparatus so that the directions of capacitive heating and external irradiation would cross in the body at right angles. Some case reports stated problems originating from increased damage to normal skin in clinical SRH applications (7). We tried to raise the TGF by irradiating only the heated target volume and avoiding irradiation of heated normal tissue. Application of our SRH method enabled us to avoid serious damage to normal skin.

Capacitive heating is a method using radiofrequency-wave transmission between 2 electrodes. These waves generate a powerful electromagnetic field inside the body and heat it. SRH

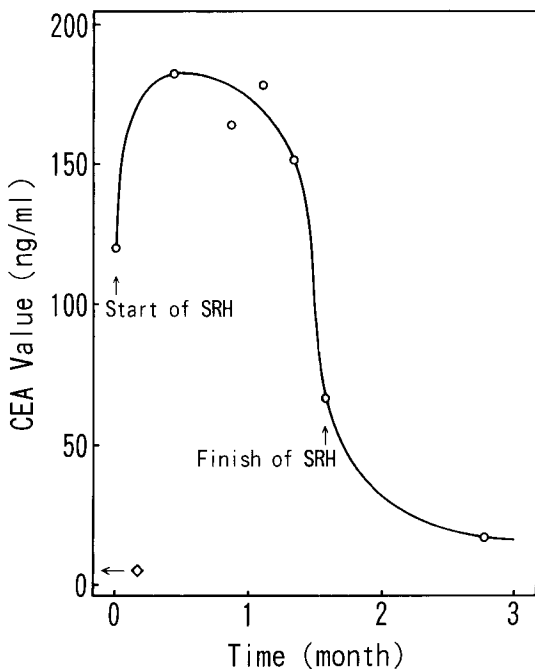


Fig. 8 CEA level changes. \diamond , Normal upper limit (5 ng/ml) of CEA. Toward the end of the treatment CEA decreased markedly and fell to an even lower value 1 month after treatment.

simultaneously uses ionizing radiation to irradiate the electromagnetic field in the body. However, interferences between both devices during SRH have not yet been thoroughly studied. In the present study we used phantoms to confirm the safety of SRH preceding its clinical application. The influence on radiation energy and flatness during operation of the capacitive heating device does not pose any clinically significant problems for SRH. Neither does operation of an external irradiation device influence the rise of temperature or distribution during capacitive heating. The above outlined results show that clinical application according to our SRH method is safe and free of interferences, when capacitive heating and external irradiation are carried out at right angles to each other.

Results of basic studies indicate that, when localized heating of the tumor is clinically possible, SRH can be expected to yield even better tumor inhibiting results (4, 17). Overgaard or Arcangeli *et al.* reported heating of malignant melanoma, skin metastases and other diseases immediately after external irradiation as SRH (6-10). However, *in vivo* studies revealed greater enhancement of sensibility for irradiation during the heating ("true") than irradiation immediately before or after the heating (17). Using spheroids, Durand reported that irradiation had a greater tumor inhibiting effect during mid heating rather than at the start or end of the heating (18).

Although we could not measure the temperature inside the tumor directly, the comparatively low average treatment temperature of 41.1°C during SRH may have been a problem in our clinical SRH case. However, because we obtained therapeutic effects without side-effects, this should be an indication for further clinical research on SRH. We designed our SRH method so that directions of capacitive heating and external irradiation would cross at right angles. This method appears to be appropriate for tumors centered in the extremities or in the pelvis away from the skin. We expect this method to be therapeutic for tumors in these

areas.

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