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● *Hyperthermia Original Contribution*

HYPERTHERMIA COMBINED WITH RADIATION THERAPY FOR PRIMARILY UNRESECTABLE AND RECURRENT COLORECTAL CANCER

YASUMASA NISHIMURA, M.D.,* MASAHIRO HIRAOKA, M.D.,* KEIZO AKUTA, M.D.,† SHIKEN JO, M.D.,* YASUSHI NAGATA, M.D.,* SHIN-ICHIROU MASUNAGA, M.D.,* MASAJI TAKAHASHI, M.D.‡ AND MITSUYUKI ABE, M.D.*

Kyoto University, Kyoto 606, Japan

The value of adjuvant hyperthermia to radiotherapy in the treatment of locally advanced colorectal cancers was investigated. Between 1981 and 1989, 71 primarily unresectable or recurrent colorectal tumors were treated with radiotherapy at the Department of Radiology, Kyoto University Hospital. Of the 71 tumors, 35 were treated with radiotherapy plus hyperthermia (group I), while 36 tumors (group II) were unsuitable for hyperthermia mainly because of difficulties with the insertion of temperature probes or the thickness of the patient's subcutaneous fat (> 2 cm). The mean total radiation dose was 58 Gy and 57 Gy for groups I and II, respectively. Thirty deep-seated pelvic tumors were treated with an 8 MHz radiofrequency capacitive heating device, and five subsurface tumors were treated with a 430 MHz microwave hyperthermia system. Hyperthermia was given following radiotherapy for 30–60 min for a total of 2–14 sessions (mean 5.7). In 32 of the 35 tumors heated, direct measurement of tumor temperature was performed. For the five tumors treated with the microwave heating device, the means of the mean maximum, average, and minimum measured intratumoral temperatures were 45.4°C, 43.3°C, and 40.6°C, respectively. The corresponding values were 42.2°C, 41.3°C, and 40.3°C for the 27 tumors treated with the capacitive heating device. Effective heating of deep-seated pelvic tumors was more difficult than heating of abdominal wall or perineal tumors. The local control rate at 6 months after the treatment, which was defined as absence of local progression of the tumors, was 59% (17/29) and 37% (11/30) for groups I and II, respectively. The objective tumor response rate (complete regression plus partial response) evaluated by computed tomography was 54% (19/35) in group I, whereas it was 36% (10/28) in group II. A better response rate of 67% was obtained in the 15 tumors with a mean average tumor temperature of > 42°C. Although limitation of our current heating devices exist, the combination of hyperthermia with radiotherapy is a promising treatment modality in the treatment of locally advanced colorectal cancer.

Locally advanced colorectal cancer, Regional hyperthermia, Radiation therapy.

INTRODUCTION

Approximately 10%–20% of patients with colorectal cancer have locally advanced unresectable tumors when first diagnosed, and patients with these tumors have a very poor prognosis for survival unless the lesions can be made resectable (3, 12, 14, 20). In these patients with primarily unresectable colorectal cancer, preoperative radiation therapy (RT) has been reported to result in resectability in 39% to 68% of the patients in six different series (3, 12, 14, 20, 22). Unfortunately, however, many patients who were resected for cure still failed in the pelvic region, and the survival for those who could not be resected was dismal. The use of adjuvant hyperthermia (HT) with preoperative RT should be tested in patients with unresectable tumors in an attempt to improve the resectability and local control.

An additional situation for a trial of adjuvant HT is in patients with recurrent colorectal cancer. The local recurrence rate following radical surgery for tumors of the rectum and the rectosigmoid colon is 30%–50% if there is tumor extension through the bowel wall or in combi-

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* Department of Radiology, Faculty of Medicine.
† Research Reactor Institute.
‡ Chest Disease Institute.
Reprint requests to: Yasumasa Nishimura, M.D., Department of Radiology, Faculty of Medicine, Kyoto University, 54-Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606, Japan.

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nation with nodal involvement (22, 23). The results of RT alone in recurrent colorectal cancer are extremely poor. Ciatto and Pacini reported only three percent 5-year survival rate in 108 patients with post-surgical recurrence in the pelvis following RT alone (4). An apparent dose relationship has been demonstrated for control of recurrent colorectal cancers by RT (19), and doses must be increased to 60 to 70 Gy or more if long-term control of disease or possible cure is desired (6). The radiation tolerance of adjacent normal tissues may limit the ability to deliver such high tumoricidal doses. Therefore, the addition of HT to RT may aid in obtaining local control.

One of the most serious problems in performing clinical HT trials is the difficulty in heating deep-seated tumors including locally advanced or recurrent colorectal cancers (5). Our group has developed potential deep-heating devices by using a radiofrequency (RF) capacitive method (1), and has reported that they can heat various tumor sites to a therapeutic range in selected patients (8). In addition to the RF capacitive heating devices, a 430 MHz microwave (MW) hyperthermia system using a lens applicator, which can heat subsurface tumors with a maximum tumor depth of 5–6 cm, was developed recently (15, 17). By using the two types of heating devices, we have treated locally advanced or recurrent colorectal cancers with adjuvant HT in conjunction with RT. We report here the results of regional HT plus RT for unresectable or recurrent colorectal cancers, together with an analysis of the thermometry, tumor response, and toxicity. The results were compared with those for advanced rectal cancers treated with RT alone during the same period.

METHODS AND MATERIALS

Patients population

Between January 1981 and May 1989, 74 patients with primarily unresectable or locally recurrent colorectal cancer were registered at the Department of Radiology, Kyoto University Hospital. Although prophylactic RT following radical resection of rectal cancer and RT for metastatic lesions from colorectal cancer were undertaken during the same period, these patients were not included in this study. Of the 74 patients, five patients could not receive more than 30 Gy of irradiation because of their poor general condition, four patients received postoperative RT after resection of locally recurrent rectal cancer, and three patients received intraoperative RT after resection of primarily unresectable or locally recurrent colorectal cancer. These 12 patients were excluded from this analysis. Thus, the remaining 62 patients were enrolled in this study.

Of the 62 patients, seven patients received re-irradiation to the recurrent tumors after initial RT to recurrent colorectal cancers, one patient received re-irradiation to a pelvic wall recurrence after RT to an unresectable rectal cancer, one patient received re-irradiation to a recurrent tumor in the hip after RT to a perineal recurrent tumor, and one patient received re-irradiation to a pelvic recurrence after prophylactic RT following curative resection of a rectal cancer. Because all the 10 patients had received definitive dose irradiation to the pelvic region (50–78 Gy), re-irradiation was limited to gross disease with various techniques to minimize the dose to normal tissues. A mean total radiation dose of 46.7 Gy (range: 40–51 Gy) was given. Four of the 10 tumors were treated with RT plus HT at re-irradiation. An average interval between initial RT and re-irradiation was 12 months (range: 5–20 months).

The 71 tumors treated include 10 re-irradiated tumors, and 35 tumors in 33 patients were treated with HT in conjunction with RT (Group I). The remaining 36 tumors in 33 patients were treated with RT alone (Group II). Four patients were entered into both treatment groups because treatment modalities were different at initial treatment and re-irradiation. This study was not a randomized one, and the selection of patients for the combined treatment was based mainly on the feasibility of HT treatment. Reasons for excluding HT in group II patients were as follows: five patients were treated before the installation of an 8 MHz radiofrequency (RF) capacitive heating device* in 1983; eight patients had pelvic subcutaneous fat which exceeded 2 cm in thickness, and were not treated with HT because of potential of overheating the subcutaneous fat tissue by the RF capacitive device; nine patients had relatively small tumors that were located deep in the true pelvis which precluded the insertion of temperature probes into the tumors; seven patients were excluded because of poor general condition, disseminated disease, or advanced age (> 80 y.o.). Three patients refused HT after one trial HT session. All the three HT sessions were terminated within 30 min at the patient's request, and tumor temperatures had not reached the therapeutic temperature range, so these tumors were classified into Group II.

Table 1 shows the characteristics of the tumors in the two groups. All tumors were adenocarcinoma. Group I included seven patients with primarily unresectable colorectal cancers, while Group II included two patients with primarily unresectable rectal cancers. All patients with primarily unresectable colorectal cancers had been referred to our department after an exploratory laparotomy and colostomy had found the tumors were unresectable. All 10 patients with colon cancers were entered into the combined modality group. All the unresectable or recurrent colon tumors that invaded the adjacent abdominal wall, and readily permitted the percutaneous insertion of

* Thermotron RF8, Yamamoto Vinyter Co., Ltd. Osaka, Japan.

Table 1. Characteristics of the tumors treated

	RT + heat (Group I)	RT alone (Group II)
No. of tumors	35	36
No. of patients	33	33
State of tumors		
Primary rectal ca.	5	2
Recurrent rectal ca.	20	34
Primary colon ca.	2	0
Recurrent colon ca.	8	0
Tumor volume (cm^3)	195 ± 37*	49 ± 8†
Total RT dose (Gy)	58 ± 1.7	57 ± 1.3
(range)	(40–70)	(40–70)
Previous RT	4	6
(range, Gy)	(59–78)	(50–67)
No. of hyperthermia	5.7 ± 0.4	—
(range)	(2–14)	
Chemotherapy	3	3

RT = Radiation therapy.
* Mean ± standard error.
† Group I vs. Group II; $p < 0.001$.

temperature probes safely and easily, were treated with HT. These mostly subsurface tumors could be easily heated to therapeutic temperatures by our heating devices. Therefore, all these colon tumors were treated with HT. The mean tumor volume in Group I was significantly larger than that in Group II ($p < 0.001$). This difference was attributable to the difficulties with the insertion of temperature probes into the small tumors. The mean total radiation doses in the two groups were quite similar, and all the tumors received more than 40 Gy irradiation. Four tumors in Group I and six tumors in Group II were re-irradiation cases as mentioned above.

Both groups included three patients each who were treated with concomitant chemotherapy during the course of RT, although no specific chemotherapy protocol existed. For one patient with primarily unresectable rectal cancer in group I, 50 mg of cisplatinum (CDDP), 6 mg of mitomycin-C(MMC), and 250 mg of 5-fluorouracil (5FU) were administered during HT treatment, with an additional 500 mg of 5FU given in the following 2 days. For another patient with recurrent colon cancer in group I, 10 mg of adriamycin (ADR), 3 mg of MMC, and 500 mg of 5FU were administered on the day of HT, and the same regimen was repeated again 1 week later. For the remaining patient in group I, 10 mg of MMC was given during the course of RT, but not on the day of HT. For group II, one patient received two courses of combining chemotherapy of 8 mg of MMC and 2400 mg of 5FU. 5FU was administered by continuous drip infusion for 72 hr in this patient. Another patient in group II received four courses of 50 mg of CDDP with 1 week interval between doses. The remaining patient in group II was treated with 15 mg of ADR and 3 mg of MMC once during the course of RT.

Hyperthermia equipment

Two different devices were used in this study. An 8 MHz RF capacitive heating device, which has two metal plates placed on opposite side of the tissue volume to be heated and connected to an 8 MHz RF generator, was used in the treatment of the pelvic deep-seated tumors (1). In most cases, a 25-cm electrode was paired opposite either a 25-cm or 21-cm electrode. An overlay bolus, through which salt solution controlled at 5°C was perfused, was inserted between the electrodes and the body to avoid the edge heating effect and excessive heating of subcutaneous fat (24).

For more superficial sites, for example abdominal wall recurrence of colorectal cancer, a 430 MHz microwave (MW) hyperthermia system with a lens applicator† was used. The MW hyperthermia device was installed at our department in 1988, and five recent subsurface tumors were treated with it. This heating system was developed to increase the penetration depth of MW by use of a lens applicator. A four-aperture lens applicator with total aperture size of 21 × 8 cm with three metal plate inside it was used. These metal plates control the phase of the electromagnetic field in the aperture, and produce a convergent MW effect (15, 17). Our initial clinical results with the 430 MHz MW hyperthermia system revealed good heating of localized subsurface tumors with a maximum tumor depth of 5–6 cm (17).

Hyperthermia and temperature measurement

Hyperthermia was applied 10–30 min after RT once a week for a total of 2 to 14 sessions (mean 5.7 sessions), although in some early cases HT was applied twice weekly. We intended to treat tumors with at least five HT sessions. However, 10 tumors were treated with less than five sessions because of a short total treatment period in five cases, inadequate heating in four cases, and patient's refusal in one case. In each HT session, we tried to maintain all monitored tumor temperatures above 42°C for 30–40 min. However, it was not possible to achieve the intended treatment temperature in most cases. Therefore, we administered HT at the maximum power tolerable by the patient, and terminated after the power had been on for 40–60 min. The blood pressure and pulse rate were monitored during HT.

For the 35 tumors in group I, 178 HT sessions were performed using the RF capacitive heating device for 32 tumors, and 23 HT sessions were done by the MW heating device for five tumors. Two abdominal wall recurrent tumors were treated with the RF heating device initially. However, the two patients refused treatment by the device

† HTS-100, Tokimec, Tokyo, Japan.

because of heat pain after one or two HT sessions, respectively. So, the following five or four HT sessions for the tumors were given by the MW heating device. These two tumors were classified as tumors treated by the MW heating device in the evaluation of tumor response.

Temperature was measured using a single-point or multipoint microthermocouple sensor, which was inserted into the tumor through a 21-gauge catheter. Because most tumors were located deep in the pelvic cavity, it was clinically impossible to insert many catheters into the tumors. Therefore, only one or two catheters were inserted into a tumor as deeply as possible either transcutaneously or through the anus, with the aid of ultrasound, computed tomography (CT), or by palpation. For two patients with unresectable or recurrent colorectal cancers, catheters for thermometry were inserted at laparotomy.

Of the total 201 HT sessions, direct measurements of intratumoral temperature were performed in 169 HT (84%) sessions for 32 tumors. During 115 of the 169 HT sessions, the thermal distribution within the tumor was obtained by moving a thermal sensor (87 sessions) or a multipoint sensor (28 sessions). On the other hand, only one point in a tumor was monitored in the remaining 54 sessions.

For the MW heating device, tumor temperatures were monitored every 24 seconds at 3–6 points (mean 4.3) by multipoint sensors (17). However, for most HT treatments by the RF heating device, a single-point sensor was used. In this case, a temperature of the deepest point from the surface was monitored continuously, and thermal distribution within a tumor and the surrounding normal tissue was obtained by moving the sensor at 1 cm intervals along each catheter track. Temperature maps were usually obtained twice at 15–25 min after the start of treatment and at the end of treatment because tumor temperatures equilibrated within 20 min of the treatment in most cases. Thermal maps were done immediately after turning off the RF power, because most insertion points of thermal probes were covered by the large electrodes and the overlay bolus. Therefore, frequent thermal mapping was not possible in this study. The mean and standard deviation of the intratumoral mapping points for each treatment were 5.8 ± 3.1 with a range of 2 to 17.

Definition of thermal parameters

For the analysis of thermal data obtained, several thermal parameters were defined as follows.

1. Tmax, Tmin, and Tav are the maximum, minimum and average temperatures of all recorded intratumoral temperatures during a steady state and at the end of treatment. A steady state was defined 10 min after the start of HT for the MW heating device, and 20 min after the start of HT for the RF heating device, even if the temperatures showed slight gradual increase in some tumors.

2. F(41°C) is a sampling fraction of the thermal mapping temperature measurements at the end of treatment which exceeded 41°C within a particular thermometry probe tract.

Tav was both a spatial and temporal average in 115 HT sessions in which thermal distributions were obtained, although Tav was just a temporal average in 54 HT sessions in which tumor temperatures at a single tumor point could be monitored. In the latter case, Tmax, Tmin and F(41°C) could not be obtained.

All the parameters were determined for each HT session, and averages of these parameters were calculated over all treatments for a given tumor ($\overline{\text{Tmax}}$, $\overline{\text{Tmin}}$, $\overline{\text{Tav}}$, $\overline{\text{F(41°C)}}$). In addition, we defined a HT session as effective when any intratumoral temperature exceeded 42°C for more than 20 min. We did not calculate a thermal dose as equivalent time at 43°C because continuous multipoint thermometry was available for only five tumors treated with the MW heating device. Figure 1 shows the temperature profile of a recurrent rectal cancer treated with the 8 MHz RF capacitive heating device.

Radiation therapy

Irradiation was mainly delivered by a 10 MV linear accelerator, although a cobalt-60 apparatus and electron

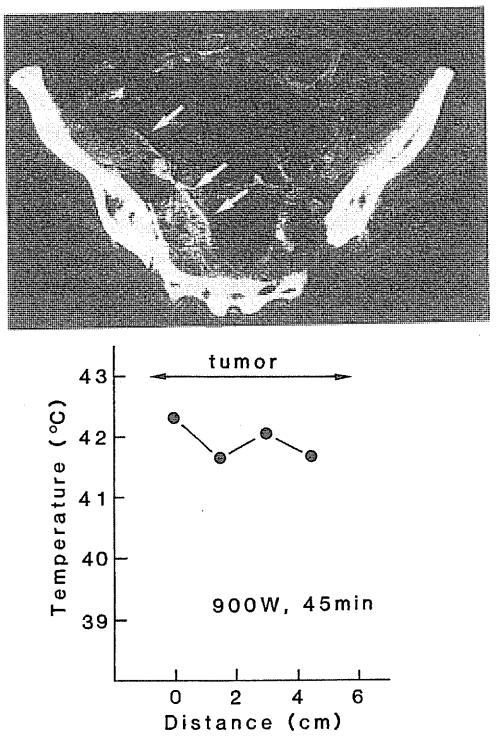


Fig. 1. The temperature profile of a recurrent rectal tumor in the true pelvis. A catheter for a thermometry probe (arrows) was inserted at laparotomy into the deepest portion of the tumor. This temperature profile was obtained at the end of 50 min heating with the Thermotron RF8. In this particular heat session, Tmax, Tav, Tmin, and F(41°C) were 42.4°C, 41.9°C, 41.5°C, and 100%, respectively.

beams were used for some tumors. In the majority of the patients, an irradiation dose of 40–50 Gy was given through anterior-posterior portals encompassing the tumor with a margin, and a 10–20 Gy boost dose delivered to the tumor with various techniques. Except for one tumor, a conventional fractionation scheme was used; that is, 1.6–2.1 Gy per day, 5 days a week, to a total dose of 40–70 Gy.

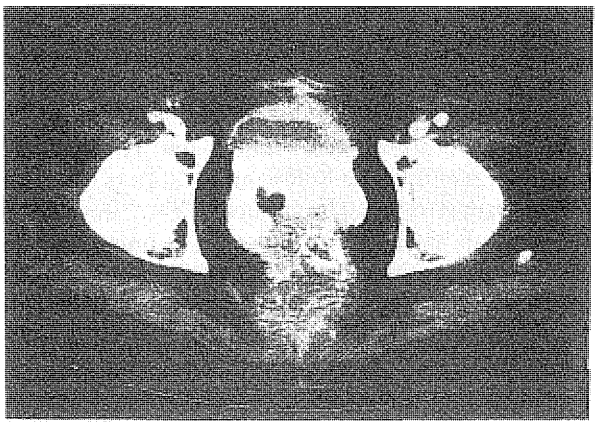
Evaluation of tumor response

The change in tumor volume was determined mainly by CT scan, which was performed every 2–3 months after treatment. Tumor response was evaluated both when the tumor showed maximum regression and when the regression had continued for more than 4 weeks. Grading of tumor response was as follows: complete tumor regression was designated as complete regression (CR), 50–99% regression in volume as partial regression (PR), and less than 50% regression as no regression (NR).

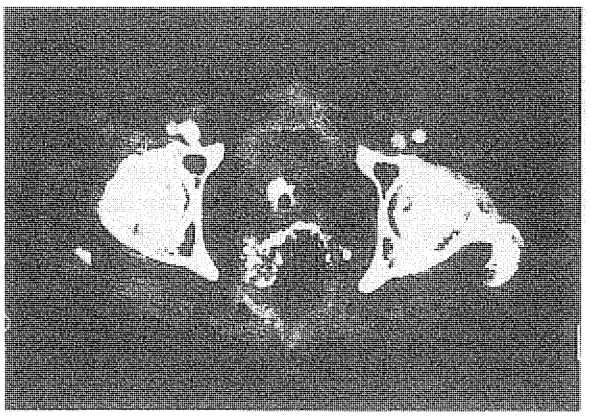
For intrapelvic colorectal tumors, distinguishing tumor tissues from fibrotic scars by CT scan is often quite difficult. In addition, some effectively heated tumors showed an intratumoral low density area on post-treatment CT scan (Fig. 2). These tumors can remain at the same tumor volume without progression for long time (17). Therefore, the local control was also evaluated in this analysis. Local control was defined as the absence of local tumor progression based on clinical and roentgenological examinations.

Statistics

Following Snedecor's F-test, the Student's t-test or Welch's t-test was used to assess the significance of difference. Chi-squared test was also used.



(a)



(b)

Fig. 2. (a) CT scan of a recurrent rectal cancer invading the bladder. This tumor received a total of 66 Gy of irradiation in combination with 14 sessions of RF capacitive hyperthermia ($\overline{Tav}$ = 43.9°C). (b) Although no tumor regression was noted 3 months after the combined treatment, a marked low density area was demonstrated by CT scan. Needle biopsy performed at this time revealed coagulation necrosis and fibrosis, without any viable tumor cells. This tumor had not regrow by 10 months after the treatment when the patient died of distant metastases.

RESULTS

Thermometry results

Our treatment goal of HT, that is Tmin of > 42°C for > 30 min, was achieved only in 15 HT sessions (13%) of the 115 sessions in which thermal distributions were obtained. If we defined HT sessions as effective when any intratumoral point exceeded 42°C for > 20 min, 90 HT sessions (53%) of the 169 sessions in which direct tumor temperature measurement was done were effective. Tav of more than 42°C was achieved in 15 (47%) of the 32 tumors.

Significant difference in thermal parameters excluding $\overline{Tmin}$ was noted between the two heating devices. The mean of $\overline{Tmax}$, $\overline{Tav}$, $\overline{Tmin}$, and $\overline{F(41°C)}$ for the five subsurface tumors treated with the HTS-100 were 45.4°C, 43.3°C, 40.6°C, and 90%, respectively. Similarly, the value were 42.2°C, 41.3°C, 40.3°C, and 60% for the 27 deep-seated tumors treated with the 8 MHz RF heating device. Table 2 shows the thermal parameters according to the treatment site. Tumors located in the abdominal wall or hip were the most easily heated, followed by tumors in the perineum. It was difficult to heat tumors located in the true pelvis or in the para-aortic region.

Tumor response and local control

Tumor response and local control in the treated volume were analyzed according to treatment modality. Table 3 shows the local control rates in the two treatment groups. The local control rates were 59% at 6 months and 31% at 12 months after treatment for group I, while the corresponding values were 37% and 22% for group II. The difference in the local control rates between the two groups were not statistically significant. Three tumors in group I were radically resected after the combined treatment because of the regression of the tumors. If we regard the

Table 2. Temperature parameters for each treatment site

Treatment site	Temperature parameters			
	$\overline{Tmax}$ (°C)	$\overline{Tav}$ (°C)	$\overline{Tmin}$ (°C)	$\overline{F(41°C)}$ (%)
Abdominal wall and hip* (n = 8)	44.2 ± 2.1†	42.6 ± 1.3	40.5 ± 0.7	86 ± 10
Perineum (n = 5)	43.1 ± 1.7	42.2 ± 1.2	40.5 ± 1.1	53 ± 33
Pelvis (n = 18)	42.1 ± 1.5	41.2 ± 1.5	40.1 ± 1.1	54 ± 34
Paraaorta (n = 1)	39.4	39.0	38.6	0

* All of the five tumors treated with the MW heating device were classified into this subgroup.
† Mean ± standard deviation.

three tumors as being locally controlled, the local control rates for group I were 63% at 6 months and 38% at 12 months.

Objective tumor response could be evaluated in 35 tumors for group I and 28 tumors for group II, excluding eight group II tumors without posttreatment CT scan. In group I, four tumors (11%) exhibited CR, and 15 tumors (43%) exhibited PR (total of 54%). The four CR cases were: one primarily unresectable rectal cancer, one locally recurrent rectal cancer, one post-RT recurrent rectal tumor in the hip region, and one abdominal wall recurrence of colon cancer. None of these tumors have shown local recurrence in follow-up periods of 26, 36, 30, and 1 month, respectively. One patient with an abdominal wall recurrence of colon cancer died of intestinal perforation 1 month after treatment, and at autopsy no malignant cells were found in the abdominal wall histologically. The intestinal perforation had occurred after intestinal obstruction of 2 to 3 months because of the involvement of an intestine loop by tumor. Although the site of the perforation was not identified by autopsy, no sign of heat damage was noted in the intestinal loop pathologically. Fifteen PR tumors in group I consisted of four primarily unresectable colorectal cancer, six locally recurrent rectal tumors in the true pelvis or perineum, three recurrent colorectal cancer in the abdominal wall, and two cases of para-aortic lymph nodes metastasis from colon cancer. Two of the four primarily unresectable colorectal cancers were finally resected radically as the tumors regressed with the combined treatment. In both cases, histological study of the resected specimen revealed fibrosis and necrosis of the tumor, with several clusters of degenerated tumor cells found in the muscular layers. In addition, another primarily unresectable rectal cancer, for which tumor response was NR, could be resected radically following the combined treatment. In this tumor, viable tumor cells were noted in the resected specimen.

In group II, two tumors (7%) showed CR. Both of the tumors were recurrent rectal cancer, and both have not shown local recurrence in follow-up periods of 13 and 30 months, respectively. Eight tumors (29%) showed PR. There were six locally recurrent rectal tumors, and two cases of pelvic and inguinal lymph nodes metastasis.

Table 4 shows tumor response by type of the tumors in the two groups. The tumor response rate (CR + PR) was 54% for Group I and 36% for Group II but the differences were not significant. Primarily unresectable colorectal cancer in group I showed a better response rate (71%) than those in Group II. On the other hand, the response rate of recurrent tumors in Group I were not so different from those in Group II. Although the number of re-irradiated tumors were small, better responses were observed in group I. Out of four re-irradiated tumors in Group I, one showed CR and another PR. However, no responders were noted in three Group II tumors.

Table 5 shows the tumor response rate according to the total radiation dose. In Group II, only two tumors

Table 3. Local control rate*

Treatment	RT + heat (Group I)	RT (Group II)
No. of tumors	35	36
At 6 months	17/29 (59%)	11/30 (37%)
At 12 months	8/26 (31%)	6/27 (22%)
No. of tumors resected	3	0
Follow up lost or, drop out case†	3	6

* Local control was defined as absence of local progression.
† Drop out case: patients who died within 6 months after treatment without tumor progression.

Table 4. Tumor response by type of the tumors

Type of tumors	Tumor response			
	CR	PR	NR	CR + PR
Group I (RT + heat)				
Primary tumors	1	4	2	71% (5/7)
Recurrent tumors	2	10	12	50% (12/24)
Re-irradiated tumors	1	1	2	50% (2/4)
Total	4	15	16	54% (19/35)
Group II (RT)				
Primary tumors	0	0	2	0% (0/2)
Recurrent tumors	2	8	13	43% (10/23)
Re-irradiated tumors	0	0	3	0% (0/3)
Total	2	8	18	36% (10/28)

Table 5. Tumor response according to total radiation dose

Total radiation dose	Tumor response			
	CR	PR	NR	CR + PR
Group I (RT + heat)				
40–49 Gy	1	2	3	50% (3/6)
50–59 Gy	1	2	3	50% (3/6)
60–70 Gy	2	11	10	57% (13/23)
Group II (RT)				
40–49 Gy	0	1	1	50% (1/2)
50–59 Gy	0	1	5	17% (1/6)
60–70 Gy	2	6	11	42% (8/19)

showed PR out of eight tumors which received less than 60 Gy. On the other hand, six responders including two CR cases were obtained in 12 tumors that received less than 60 Gy in the combined treatment group. In this moderate radiation dose range, HT may have increased the response rate.

Table 6 shows the response rate according to $\overline{Tav}$ of the tumors. A higher response rate of 67% was observed in the 15 tumors with a $\overline{Tav}$ of more than 42°C compared with 17 tumors with a $\overline{Tav}$ of less than 42°C, although the differences were not significant. Table 7 shows the response rate according to the heating devices. All five tumors treated with the MW heating device responded objectively. Although the response rate apparently related to the heating device, the difference between the devices was not statistically significant ($p < 0.10$), this difference may be attributable to smaller tumor volume and better heating parameters in the five tumors treated with the MW heating device.

Table 8 shows the tumor response according to number of effective HT sessions. Four CR cases received one to five effective HT sessions. The highest response rate was obtained by three to five effective sessions, but more than five effective session did not increase the response rate.

One interesting feature of the response of effectively heated tumors was the appearance of an intratumoral low density area on post-treatment CT scan (5, 12). Two locally recurrent rectal tumors, both of which achieved a $\overline{Tav}$ of more than 43.5°C, showed a homogenous low density of the whole tumor on CT scans performed at the end of thermoradiotherapy (Fig. 2). This CT change apparently depended on the achievement of adequate thermal parameters (7, 16). On follow-up, one tumor regressed slowly 3 months after treatment and the other remained stable without regrowth until the patient died of distant metastasis 10 months after treatment.

Table 6. Tumor response according to $\overline{Tav}$

Treatment	Tumor response			
	CR	PR	NR	CR + PR
Group I (RT + heat)				
$\overline{Tav} > 42$°C (n = 15)	3	7	5	67% (10/15)
$\overline{Tav} < 42$°C (n = 17)	1	7	9	47% (8/17)
No thermometry (n = 3)	0	1	2	33% (1/3)
Total	4	15	16	54% (19/35)
Group II (RT)	2	8	18	36% (10/28)

Table 7. Tumor response by heating devices

Heating device	Tumor response			
	CR	PR	NR	CR + PR
8 MHz RF capacitive	2	12	16	47% (14/30)
430 MHz MW	2	3	0	100% (5/5)

Toxicity

Table 9 shows the acute and chronic toxicity of RT with or without HT. One of the most common acute problems that occurred during RF capacitive HT was pain at the field edge or under the electrodes. Approximately 50% of the patients complained of such pain. Nine HT sessions for four patients were terminated within 30 min of heating because of the pain. Fat necrosis was observed in two patients following RF capacitive HT, and blisters occurred in one patient by MW HT. The fat necrosis disappeared spontaneously about 1 month after treatment, and the blisters healed within a few days.

Another adverse effect of HT was local infection or abscess, which were mainly caused by the contamination via the catheters inserted into the tumors. No thermal enhancement was observed for acute skin reaction by RT, which may be attributable to the use of surface cooling. A vesicorectal fistula occurred in one patient with a primarily unresectable rectal tumor invading the bladder during the course of thermoradiotherapy. This fistula seemed to be caused by the massive destruction of the tumor by the combined treatment.

In the chronic phase, the rate of intestinal damage including obstructive ileus, fistula, and perforation was higher in Group I than in Group II. As all the 10 colon cancer patients were treated with the combined treatment in this study, the rate of intestinal damage might be increased in group I. Unresectable or recurrent colon cancer invading the abdominal wall inevitably involved intestinal

Table 8. Tumor response by number of effective* heat sessions in group I tumors

No. of effective heat session	Tumor response			
	CR	PR	NR	CR + PR
0	0	4	5	44% (4/9)
1–2	1	3	4	50% (4/8)
3–5	3	6	3	75% (9/12)
6–13	0	1	2	33% (1/3)

* Any intratumoral point above 42°C for more than 20 min.

Table 9. Toxicity of radiation therapy with or without hyperthermia

	Group I (RT + heat)	Group II (RT)	Re-irradiated tumors
No. of tumors	31	30	10*
Acute phase			
Heat pain	13	—	2
Fat necrosis	2	—	0
Burn and blisters	0	—	1
Local infection	5	2	0
Rad. dermatitis	5	10	1
Leukopenia†	1	3	0
Vesicorectal fistula	1	0	0
Chronic phase			
Obstructive ileus	7	1	0
Intestinal fistula	3	0	0
Intestinal perforation	2	0	0
Bladder bleeding	0	0	3

* Including 4 tumors treated with radiation plus hyperthermia.
† $< 1500/mm^3$.

loops, which caused chronic obstruction of the intestine. Three of seven obstructive ileus cases occurred in the patients with recurrent colon cancer, and intestinal perforation occurred in two. Two other cases of obstructive ileus were noted in patients with rectal cancer who had received pelvic extirpation before or after thermoradiotherapy. No patients in Group II received pelvic extirpation. However, there exists the possibility that bowel damage had been enhanced by regional HT, because no cooling of the intestinal loop was possible.

Among 10 re-irradiated cases, three patients developed bladder bleeding 6–12 months after the re-irradiation. Two of the three patients had been treated with HT either at initial RT or at re-irradiation. Because the tumor had invaded the bladder, the posterior wall of the bladder received nearly 100 Gy in total. The tumors were not controlled at the time of bleeding, so it was unclear whether the bleeding came from the tumors or from the normal bladder. However, no other serious complications were observed in the remaining seven patients received re-irradiation.

DISCUSSION

Over the past decade, a large number of Phase I, II, and III clinical trials have been undertaken to define the toxicity and therapeutic efficacy of HT. In superficial tumors, high response rates and prolonged tumor control have been obtained with the use of HT as an adjuvant to RT (13, 18). However, information on the effects of combined HT and RT of deep-seated tumors including advanced or recurrent colorectal cancers is scanty due to the problems associated with deep heating (10, 18). Although some Phase I trials for deep-seated tumors included advanced colorectal cancers (9, 16, 21), site-specific studies on locally advanced colorectal cancers are quite few. Recently, Berdov and Menteshashvili (2) reported a Russian Phase III trial for locally advanced rectal cancer. They compared preoperative combined treatment with preoperative RT alone, and demonstrated a significant improvement in tumor response and 5-year survival rate.

There are still many problems with performing HT at the present time. One of the most critical is the inadequacy of existing deep-heating techniques. None of the presently available deep-heating techniques has universal applicability to all anatomical sites (5). Temperature measurement of the deep-seated tumors is another problem, and thermometry data obtained tend to be very limited. In our thermometry results, $\overline{Tav}$ of more than 42°C was achieved in 47% (15/32) of the patients, and the treatment goal of HT was achieved in only 13% (15/115) of HT sessions. Considering that some obese patients with more than 2 cm subcutaneous fat in the pelvic region were excluded from the combined treatment group, the above thermometry results might still be far from satisfactory. If we see the thermal parameters according to the treatment sites, tumors located in the abdominal wall were heated quite well by either the RF capacitive heating device or the MW heating device (Table 2), and those in the perineum could be heated fairly well by the RF heating device. However, adequate heating of tumors located deep in the true pelvis were quite difficult to achieve. Although the mean of the thermal parameters were a little bit disappointing among the treated pelvic tumors, some of them showed fairly good thermal parameters. Therefore, the RF capacitive heating method appeared to be worthwhile to use to heat these pelvic deep-seated tumors. It is essential to develop better deep-heating methods to treat such deep-seated tumors.

Both the tumor response rate and the local control rate were better in the combined treatment group than in the RT alone group (Tables 3 and 4), although not significantly. The response rate of tumors with $\overline{Tav}$ of > 42°C was higher than that of tumors with $\overline{Tav}$ of less than 42°C or tumors treated with RT alone (Table 6). This encouraging result strongly supports the future utility of HT as an adjuvant to RT for the treatment of locally advanced colorectal cancers.

Although in this study the number of primarily unresectable rectal cancers was small, these locally advanced rectal cancers responded very well to the combined treatment. Of the seven primarily unresectable colorectal cancers treated with thermoradiotherapy, one tumor showed CR, four PR. Two PR tumors and one NR tumor could be resected radically after combination therapy. On the other hand, two tumors treated with RT alone showed NR in both cases. In general, truly locally inoperable tumors are rarely converted to resectable tumors by mean of RT alone (14, 20). As shown in the Russian Phase III trial (2), preoperative RT combined with HT seems to be a promising treatment modality to test for unresectable rectal cancers. On the other hand, in the recurrent colorectal cancers no substantial increase in tumor response rate was observed in this study (Table 4). This unexpected

result seems attributable to the poor heating efficacy for the true pelvis tumors. In our experience, locally recurrent rectal tumors located in the presacral area, where rectal cancers recur frequently, is one of the most difficult treatment sites to heat. Another reason is the difference in the tumor volume between the two groups. Small recurrent tumors in the pelvis were entered into the RT alone group because insertion of thermometry probes into the small tumors was difficult. As the response rate of locally advanced colorectal cancers by RT depends on the tumor size (19), a thermal enhancement effect in tumor response may be obscured in the present study.

After moderate total radiation doses ranging from 40 Gy to 59 Gy, the combined treatment showed better tumor response than RT alone (Table 5). One CR case was observed out of four re-irradiated tumors by combining 50 Gy irradiation with five HT sessions. For these heavily pretreated tumors, thermoradiotherapy was a good treatment modality. Although an effect of HT was observed at moderate radiation doses, we consider that a definitive total dose (> 60 Gy) is necessary to achieve local control of advanced colorectal cancer. Because it was difficult to heat the whole tumor sufficiently using presently available heating devices, the response rate obtained was still not optimal.

Some investigators have shown no difference in tumor response between two and six HT treatments for superficial tumors (11, 18). The number of successful HT fractions required to yield a good result may depend on the ability to achieve successful tumor heating. Even one "good" HT session, a treatment sufficient to kill all clonogenic tumor cells in an environment including chronic hypoxia and increased acidity, may be sufficient for thermoradiotherapy. However, in the present study, the best response rates were achieved by three to five effective HT treatments, while more than five HT sessions did not further increase the response rate (Table 8). Although a good response might be achieved with one or two satisfactory HT treatments for superficial tumors (11, 18), four or five HT treatments may be necessary for the treatment of deep-seated tumors because of the incompleteness of the presently available deep-heating devices to heat these deep tumors.

The patients tolerated an average of six HT treatments, and acute toxicity of HT was not serious. However, local infection caused by insertion of thermal probes and chronic bowel damage appeared to be increased by HT (Table 9). Chronic bowel damage was an especially serious problem, because it was impossible to cool the bowel during regional HT. In addition, since all of the patients in this study were initially treated surgically, adhesions and bowel immobility may have enhanced bowel damage produced by thermoradiotherapy. Long-term follow-up of the complications of combined treatment is necessary in future Phase II or III studies, and randomized prospective studies for the HT plus RT protocol is needed to evaluate efficacy of therapy for the primarily unresectable and recurrent colorectal cancers.

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