CLINICAL RESULTS USING 8 Mhz RADIOFREQUENCY CAPACITIVE HYPERTHERMIA AND RADIOTHERAPY FOR RECURRENT BREAST CARCINOMA

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A clinical investigation has been conducted in recurrent and/or advanced breast carcinoma to determine the safety and effectiveness of 8 Mhz radiofrequency capacitive hyperthermia using the Thermotron rf-8.

PATIENTS AND METHODS: Since 1988, a total of 46 patients have been enrolled in this investigation. All patients had biopsy confirmed histological proof of recurrence and/or were considered to have advanced breast carcinoma. The probability for local control with radiation alone was estimated to be 5 and 25%. All radiation therapy was delivered using 4, 6, 18, or 21 MeV linear accelerator. The choice of beam type and energy was dependant on tumor location, prior radiation dose, and the limiting adjacent normal tissues. Median radiation dose of 50.4 Gy was delivered in 5-6 weeks using 1.8-2.0 Gy daily 5 times weekly. The hyperthermia treatment objective was to deliver 42.0-44.0 degrees C for 45-50 minutes per session twice weekly with a median total of 10 sessions during the above referenced radiation schedule.

RESULTS: A total of 46 patients were eligible for treatment response analysis. A total of 43 patients achieved complete tumor resolution (93.5%) out of 46 cases. There were a total of seven patients who chose to undergo tissue biopsy for a suspected residual nodule, and all seven of these patients were found to have achieved pathological CR. The minimum follow-up was three months and longest follow-up was over 60 months (median of 20 months). There were no significant side effects other than a moderate degree of pain sensations felt by some which required electrode-skin contact adjustments and/or appropriate analgesic medication.

CONCLUSIONS: These results show complete responses to a range of radiation doses without serious complications, and suggest that the use of the Thermotron RF-8 capacitive hyperthermia system in combination with conventional radiotherapy is safe and effective on the chest-wall breast cancer recurrences.

Clinical Results Using 8MHz Radiofrequency Capacitive Hyperthermia and Radiation

TABLE II. Group 1 - Eligible Patients for Treatment Response Analysis. Patient Characteristics, Radiation & Hyperthermia Parameters, and Tumor Response in Recurrent and/or Advanced Breast Carcinoma

Case ID & Age	Tumor Size Dimensions (cm) L x W x D	Radiation Total/ Frac (Gy)	Maximum Tumor Temperatures (°C)				Tumor Respon.	Follow-up (months)
			42	43	44	45		
001LKC74	8.0 x 8.0 x 8.0	50.4/ 1.8	1	4	6		CR	32
002GCM70	11.0 x 8.7 x 6.0	50.4/ 1.8		1	8		CR	15
003LF70	15.0 x 9.3 x 6.0	59.1/ 2.0		4	9		CR	12
004NO44	3.0 x 4.0 x 4.0	40.0/ 2.0			5	4	CR	5
005EAH52	8.0 x 8.0 x10.0	50.4/ 1.8		2	6	1	CR	7
006KMJ57	8.0 x 6.0 x 7.0	59.7/ 1.7			6	6	CR	21
007MAE54	6.0 x 6.0 x 2.5	36.0/ 2.0				7	CR	9
008FF64	1.5 x15.0 x 3.0	66.6/ 1.8		2	4		CR*	53
009MSR46	6.0 x 5.0 x 3.0	45.0/ 1.8		2	8		CR	42
010MLB61	4.5 x 2.0 x 3.0	43.2/ 1.8	1	9			CR	20
011CAB46	6.0 x 8.5 x 4.0	50.4/ 1.8		7	3		CR	27
012WEM59	6.0 x 5.0 x 3.0	50.4/ 1.8		7	4		CR	18
013HJ61	6.0 x 5.0 x10.0	50.4/ 1.8		1	12		PR	16
014IWD82	7.0 x 3.5 x 5.0	45.0/ 1.8			11		CR	19
015JB78	5.0 x 4.0 x 5.0	55.0/ 2.0			13		CR	6
016HMW69	6.0 x 5.6 x 4.0	61.2/ 1.8		7	3		CR	13
017GAL48	9.0 x 4.0 x 4.0	64.0/ 2.0			12		CR	30
018RMF74	11.0 x10.0 x 8.5	64.0/ 2.0		1	15	1	CR*	60
019ALW67	5.0 x 5.0 x 4.0	50.0/ 1.8		3	7		CR	20.5
020CF38	4.0 x 4.0 x 2.5	36.0/ 1.8		2	8		CR*	24
021MAH59	4.0 x 4.0 x 3.0	41.4/ 1.8			10		CR*	13
022KMR74	11.0 x 7.0 x 7.0	50.4/ 2.0			10		CR	17
023LRD47	7.0 x 5.0 x 2.5	39.6/ 1.8			11		CR	14
024PAM54	9.0 x 4.5 x 4.5	45.0/ 1.8		2	10		CR	8

TABLE II - continuation

Case ID & Age	Tumor Size Dimensions (cm) L x W x D	Radiation Total/ Frac (Gy)	Maximum Tumor Temperatures (°C)				Tumor Respon.	Follow-up (months)
			42	43	44	45		
029JPM77	15.0 x 12.0 x 7.0	45.0/ 1.8			15		CR	8 08/19/98
030MNW78	8.4 X 5.6 X 4.6	67.7/ 1.8		5	8		PR	13 12/28/98
031BJB72	7.0 x 6.0 x 3.0	63.0/ 1.8	1	6	3		CR*	16 04/30/99
032GTP66	9.0 x 6.2 x 3.2	48.0/ 2.0			10		CR	44.0 06/13/01.
033SLS48	14.0 x 15.0 x 4.5	46.8/ 1.8	1	1	8		PR	6 dvlped brain mets.
034JMW29 1998-1999	15.0 x 9.3 x 6.0	59.1/ 1.8			16		CR*	14 - lung biopsy. died 03/29/00.
035SJO45 1999	7.0 x 6.0 x 4.0	46.0/ 2.0			10		CR	9.5 - 12/09/99. brain mets/died 02/10/00.
036JBH52 1999	4.5 x 4.5 x 4.5 area microcp tumor cells.	48.0/ 2.0			10		CR	18
037MLA49 1999	7.0 x 7.0 x 2.0	50.4/ 1.8			12		CR	3
038ESB78	10.0 x 8.0 x 3.5	50.4/ 1.8		2	7		CR	10
039BMB66 2000	10.0 x 8.0 x 5.5	64.8/ 1.8			15		CR	6
040PHD48 2000	9.0 x 6.0 x 5.5	50.4/ 1.8	6	6	1		PR	6
041PHD48 2000	4.0 x 4.0 x 3.0	50.4/ 1.8		3	9		CR	6
042DKR45 2000	10.0 x 8.0 x 4.0	45.0/ 1.8		2	8		CR	5
043SRH52 2001	12.0 x 8.0 x 4.0	66.6/ 1.8			15		CR	5
044SFH69 2001	12.0 x 12.0 x 3.5	39.6/ 1.8			7		CR	5.5 03/08/02.
045NCM50 2001	18.0 x 6.0 x 4.5	45.0/ 1.8			10		CR	12 04/09/02.
046NCM50 2001	10.8 x 6.0 x 4.5	45.0/ 1.8			10		CR	12 04/09/02.

TABLE III. Group 2 - Ineligible Patients for Treatment Response Analysis. Patient Characteristics, Radiation & Hyperthermia Parameters, and Tumor Response in Recurrent and/or Advanced Breast Carcinoma

Case ID & Age	Tumor Size Dimensions (cm) L x W x D	Radiation Total/ Frac (Gy)	Maximum Tumor Temperatures (°C)				Tumor Respon.	Follow-up (months)
			42	43	44	45		
001HLB72	8.0 x 8.0 x 8.0	50.4/ 1.8			15		PR	8 weeks after, residual mass removed.
002KMJ42	6.0 x 5.0 x 4.0	52.6/ 1.8		6	7	1	--	Patient withdrew after 4.5 weeks.
003RHT63	10.0 x 5.0 x 3.0	52.2/ 1.8		10			CR	Noncompliant after 4 weeks.
004NMV54	9.0 x 4.5 x 4.5	32.4/ 1.8	3	3	2		NR	Patient withdrew after 4 weeks.
005JMS68	10.0 x10.0 x 5.6	60.0/ 1.8		2	3		PR	Patient withdrew after 2 weeks.
006TIC85	7.3 x 6.0 x 4.6	50.0/ 2.0		1	6	1	PR	Patient withdrew after 2.5 months.
007VEB74	4.5 x 4.0 x 5.0	50.4/ 1.8			8		PR	Patient withdrew after 2 months.
008EMR43	7.0 x 6.0 x 5.8	44.5/ 1.65			11		PR	≤ 2 month follow-up.
009BJS65	3.0 x 3.0 x 2.5	6.0/ 2.0		3			-	Patient withdraw within 10 days.
010PEP87	5.0 x 5.0 x 3.5	50.4/ 2.0	1	1	11		PR	limited follow-up; expired.
011BNF50	15.5 x 11.0 x 7.0	40.0/ 2.0			11		- 09/27/99	Tx started -07/14/99.
012LRM75	8.0 x 8.0 x 4.0	40.0/ 2.5	1	5	1		withdraw 10/18/1999	pt withdrew.

TABLE IV. Distribution of maximum tolerable heating sessions achieved with the Thermotron RF-8 in recurrent and/or advanced breast carcinoma: N = 58 patients.

Temperatures	42°C	43°C	44°C	45°C
Group 1: N = 46 pts. 502 heating sessions	10 (2.0%)	92 (18.3%)	381 (75.9%)	19 (3.8%)
Group 2: N = 12 pts. 106 heating sessions	5 (4.7%)	31 (29.2%)	75 (70.7%)	2 (1.9%)
TOTAL: N = 58 pts. 608 heating sessions	15 (2.4%)	123 (20.2%)	456 (75.0%)	21 (3.4%)

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Clinical results of thermoradiotherapy for locally advanced and/or recurrent breast cancer—comparison of results with radiotherapy alone

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From August 1979 until 1988, 26 breast cancer patients with 30 tumours were treated by hyperthermia in combination with radiotherapy. Of the 30 tumours, 11 were locally advanced primary tumours (group 1), six were locally advanced recurrent tumours after operation (group 2) and 13 were locally recurrent tumours after radiotherapy (group 3). The thermal profiles showed that the capability of an RF capacitive heating device is comparatively high for large breast tumours with a volume of more than 100 cm^3, and that of a 430 MHz microwave device with a single-lens applicator is excellent for localized tumours. The response rate of group 1 and 2 tumours was excellent, and superior to that of historically controlled tumours that were treated by radiotherapy alone from July 1962 until August 1979. In group 3 the tumour response to thermoradiotherapy was not different from that to radiotherapy, but the possibility of significantly reducing total irradiation dose was indicated. More than one good heating session led to a significantly high local response, and factors having a tendency to influence local response were average minimum tumour temperature, tumour volume, and number of effective heat treatments.

Key words: Local hyperthermia, radiotherapy, thermoradiotherapy, breast cancer.

1. Introduction

Breast cancer has been treated with various therapeutic modalities, but it is not easy to control unresectable locally advanced primary breast cancer and recurrent breast cancer with conventional modalities. This paper reports our clinical results of local hyperthermia combined with radiotherapy for these tumours, and analyses thermometry, tumour response, toxicities, and factors influencing tumour response. This study is not a formal randomized trial, but the results were compared with those of historically controlled tumours treated with radiotherapy alone.

2. Materials

From August 1979 until April 1988, 26 breast cancer patients with 30 tumours were treated with thermoradiotherapy. Of the 30 tumours, 11 were locally advanced primary tumours, six locally recurrent tumours after operation, and 13 locally recurrent tumours after radiotherapy. All of the six recurrent tumours after operation had been subjected to radical mastectomy, and recurrent tumours after radiotherapy had previously received a total dose of 45–100 Gy (mean ± SD = 62·4 ± 18·5) with cobalt-60 gamma-ray or high-energy electrons, in fractions of 1·8–3 Gy, 5 days a week. All patients were female, and their ages ranged from 32 to 86 years (mean ± SD = 51·2 ± 9·8). All tumours were invasive ductal cancers. Locally recurrent tumours resisted previous chemotherapy, and appeared

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to be difficult to control with radiotherapy alone. Two primary tumours with distant metastases were treated in combination with chemotherapy.

Historically controlled tumours treated by radiotherapy alone between July 1962 and August 1979 consisted of 11 locally advanced primary tumours, 27 locally recurrent tumours after operation, and 19 locally recurrent tumours after radiotherapy. As for primary tumours, no great differences in TNM distributions (UICC classification 1987) between thermoradiotherapy and radiotherapy alone groups were observed (table 1). All recurrent tumours after operation had been subjected to radical mastectomy. To all these recurrent tumours after radiotherapy the conventional fractionation, 2–3 Gy per day, 5 days a week had been given previously, with a total dose of 37·5–50 Gy (mean ± SD = 45·9 ± 3·4) with cobalt-60 gamma-ray or high-energy electrons. Ages ranged from 24 to 86 years (mean ± SD = 54·0 ± 13·6), and all tumours were invasive ductal cancers. No tumours were treated in combination with chemotherapy.

3. Methods

We used four types of heating equipment. An 8 or 13·56 MHz RF capacitive heating device (Yamamoto Vinyter Co., Oasaka, Japan) was employed for large tumours. Localized tumours were treated by a 430 MHz microwave equipment with a single-lens applicator (Tokyo Keiki Co., Tokyo, Japan), and a 2450 MHz microwave with a multi-applicator (Minato Medical Science Co., Osaka, Japan) for superficially spreading tumours. Hyperthermia was administered once or twice a week after radiotherapy, for 30–60 min per session, up to a total of 2–10 sessions (mean ± SD = 6·1 ± 2·4). In an early study hyperthermia was administered mainly twice a week. However, in a subsequent study it was administered mainly once a week to prevent the occurrence of thermotolerance. Radiotherapy was delivered in fractions of 1·8–2 Gy a day, 5 days a week, to 54–74·4 Gy for nine of the primary tumours, to 50–61·2 Gy for all of the six recurrent tumours after operation and to 20–58 Gy for 9 of the 13 recurrent tumours after radiotherapy. The two remaining primary tumours and four recurrent tumours after radiotherapy received a total dose of 48–60 Gy and 28–44 Gy, respectively, in fractions of 4 Gy, twice weekly. Irradiation was delivered mainly with cobalt-60 gamma-ray for primary tumours and recurrent tumours after operation, and mainly with high-energy electrons or soft X-ray for recurrent tumours after radiotherapy.

As for historically controlled tumours, radiotherapy had been delivered in fractions of 2–3 Gy a day, 5 days a week, to 48–80 Gy for all of the 11 primary tumours, to 32·5–70 Gy for 25 of the 27 recurrent tumours after operation, and to 30–64·8 Gy for 16 of the 19 recurrent tumours after radiotherapy. The remaining two recurrent tumours after operation and three recurrent tumours after radiotherapy received a total dose of 60–64 Gy and 40–81 Gy, respectively, in fractions of 4–8 Gy, twice weekly. Irradiation was delivered mainly with cobalt-60 gamma-ray for primary tumours, and mainly with cobalt-60 gamma-ray or high-energy electrons for recurrent tumours.

Table 1. TNM distribution of primary tumours

TNM	HT+XRT	XRT
T3N0	2	1
T3N2		2(1)
T4N0	2	1
T4N2,3	7(1)	7(1)
Total	11(1)	11(2)

Figures in parentheses indicate recurrence or regrowth case.

Time dose fractionation factor (TDF) values of the tumours treated with thermoradiotherapy were 96·7–122·6 (mean ± SD = 108·6 ± 8·3) for primary tumours, 80·6–96·7 (mean ± SD = 89·7 ± 6·8) for recurrent tumours after operation, and 32·2–93·5 (mean ± SD = 62·7 ± 17·1) for recurrent tumours after radiotherapy. Figures for the tumours treated with radiotherapy alone were 77·4–129·9 (mean ± SD = 106·8 ± 17·4), 59·1–127·3 (mean ± SD = 98·6 ± 18·5), and 53·7–176·0 (mean ± SD = 102·8 ± 25·7), respectively. No significant difference in mean TDF between thermoradiotherapy group and radiotherapy-alone group for primary tumours and recurrent tumours after operation was observed using Student's *t*-test. On the other hand, TDF of recurrent tumours after radiotherapy in the thermoradiotherapy group was significantly lower than that in another group ($P < 0·01$).

Temperatures were measured using thin Teflon-coated microthermocouples (Sensortek Inc., NJ, U.S.A.) which are inserted into tumours through 21- or 19-gauge angiocatheters. In an early study the angiocatheters were inserted into the tumour centre and only the tumour centre temperatures were monitored. Thereafter we inserted angiocatheters into a tumour as deeply as possible, and monitored the temperature of the deepest point. Thermal profiles within a tumour were measured by moving the microthermocouple during and after the hyperthermic treatment.

Local response was graded as CR (complete response), PRa (80–99% regression), PRb (50–79% regression), and NR (less than 50% regression). Some tumours treated with thermoradiotherapy were comparatively large and had mostly disappeared, but not completely, after thermoradiotherapy. Therefore such a response could be clinically regarded as CR, and graded as PRa. The local response was evaluated as CR + PRa within 2 months after the treatment.

The follow-up period ranged from 6 to 48 months (mean ± SD = 17·7 ± 10·5) in the thermoradiotherapy group and from 6 to 149 months (mean ± SD = 35·6 ± 34·6) in the radiotherapy-alone group. The tumours that showed CR or PRa in the follow-up of 6 months were regarded as locally controlled tumours, and the local control rate was calculated. Survival rate was calculated using Kaplan–Meier's method. The statistical difference between two means were analysed using Student's *t*-test, and the statistical significance for tables was analysed using the chi-square test.

4. Results

4.1. *Thermometry*

Intratumour temperature was measured in 176 of the 182 heat treatment sessions for the 30 breast tumours. In 116 sessions for 22 tumours the thermal distribution within the tumour and surrounding normal tissue was measured. Thermal parameters were defined as follows; (1) maximum or minimum tumour temperature (T_{max}, T_{min}), that is, maximum or minimum tumour temperature at the end of treatment; (2) sampling fraction of over 42°C ($F_{(>42°C)}$), that is, the fraction of thermal mapping temperature measurements which exceed 42°C within a particular thermometry probe tract. All of these parameters were averaged over the entire course of treatment in each tumour ($\overline{T_{max}}$, $\overline{T_{min}}$, $\overline{F_{(>42°C)}}$) (table 2) (Sapozink *et al.* 1988, Shim *et al.* 1988). With a 430 MHz microwave heating device we could obtain excellent thermal profiles for localized tumours ($\overline{T_{max}} = 44·3$°C, $\overline{T_{min}} = 42·5$°C) and $\overline{F_{(>42°C)}}$ was about 80%. With this device, significantly higher values of $\overline{T_{min}}$ and $\overline{F_{(>42°C)}}$ were obtained than with any other device ($P < 0·05$). With an RF capacitive device, tumours of more than 100 cm^3 showed comparatively higher thermal parameters than tumours less than 100 cm^3 ($\overline{T_{max}} = 44·3$°C, 41·8°C, $\overline{T_{min}} = 40·4$°C, 39·8°C, $\overline{F_{(>42°C)}} = 49$%, 24%, respectively). With a 2450 MHz microwave heating device we obtained a fairly good thermal profile ($\overline{T_{max}} = 42·5$°C, $\overline{T_{min}} = 39·7$°C,

Table 2. Thermal parameters

Heating device	Tumour volume (cm^3)	$\overline{T_{max}}$ (°C)	$\overline{T_{min}}$ (°C)	$\overline{F_{(>42°C)}}$ (%)
430 MW ($n=5$)	18±14†	44·3±0·5	42·5±0·2	80±2
RF				
>100 cm^3 ($n=6$)	326±76	44·3±1·0	40·4±0·3	49±10
≤ 100 cm^3 ($n=5$)	55±10	41·8±0·4	39·8±0·4	24±9
2450 MW ($n=6$)	62±15	42·5±0·3	39·7±0·2	36±8

†Mean±SEM (standard error of the mean).

$\overline{F_{(>42°C)}}$=36%). However, these profiles were inferior to those obtained with a 430 MHz microwave device.

4.2. *Local response*

The local response rate was calculated as CR+PRa rate. The local response rates in both groups are shown in table 3. Almost all local response rates were good except for primary tumours treated by radiotherapy alone.

4.3. *Local control*

The local control rate for each tumour in the hyperthermia plus radiotherapy groups was comparatively higher than that in the radiotherapy-alone groups except for recurrent tumours after radiotherapy (table 4). Of the 13 tumours which achieved CR with thermoradiotherapy, 12 did not recur during the follow-up period. The remaining tumour, which was a recurrent tumour after radiotherapy, recurred 8 months after treatment.

4.4. *Favourable factors influencing local response*

Several variables—including total radiation dose, tumour volume and thermometry parameters—were examined in terms of their relationship to the local response or local control rates.

The mean TDF value was significantly smaller in the hyperthermia plus radiotherapy group than in the radiotherapy-alone group for the treatment of recurrent tumours after radiotherapy ($P<0·01$). Nevertheless, both groups showed a similar high local response rate (tables 3 and 5).

Table 3. Local response rate (CR+PRa)

Tumour	HT+XRT	XRT
Primary tumour	10/11 (91%)	6/11 (55%)
Recurrent tumour after operation	5/6 (83%)	24/27 (89%)
Recurrent tumour after radiotherapy	12/13 (92%)	16/19 (84%)

Table 4. Local control rate†

Tumour	HT+XRT	XRT
Primary tumour	9/10 (90%)	4/6 (67%)
Recurrent tumour after operation	4/5 (80%)	17/24 (71%)
Recurrent tumour after radiotherapy	8/12 (67%)	12/16 (75%)

†CR+PRa in the follow-up of 6 months.

Table 5. Local response of recurrent tumours after radiotherapy according to mean TDF†

Tumour response	Mean TDF		
	HT+XRT	XRT	
CR+PRa	64±17‡ (n=12)	105±27 (n=16)	$P<0{\cdot}01$
PRb+NR	45·1 (n=1)	90±1 (n=3)	$P<0{\cdot}01$

†Time dose fractionation factor.
‡Mean ± SD.

In both treatment groups the tumours smaller than 100 cm^3 exhibited a better local response than those larger than 100 cm^3 (table 6). Large tumours responded better in the thermoradiotherapy group than in the radiotherapy-alone group.

There was no relationship between local response rate and average maximum tumour temperature (table 7). Although not significantly, the average minimum tumour temperature seemed to be related to local response (table 8). Tumours heated to over 40°C in average minimum temperature showed a comparatively higher response. To assess the efficacy of heating we defined heat treatment as effective when the temperature at any point of the tumour could be maintained above 42°C for more than 20 min. According to this criterion, 125 of the 176 heat treatment sessions were effective. More than three effective heat treatments tended to lead to a higher local response than less than two (table 9). Except for one CR tumour the remaining CR tumours received more than three effective sessions. All CR and PRa tumours, except for one PRa tumour, received at least one heat session whose $F_{(>42°C)}$ was over 50%. More than one heat session whose $F_{(>42°C)}$ was over 50%

Table 6. Local response rate according to tumour volume

Tumour volume (cm^3)	HT+XRT	XRT
≤100	18/19 (95%)	40/48 (83%)
>100	9/11 (82%)	6/9 (67%)

Table 7. Local response according to average maximum tumour temperature

Average maximum tumour temperature (°C)	Local response				
	CR	PRa	PRb	NR	CR+PRa
>46		1			1/1 (100%)
44–46		2	1		2/3 (67%)
42–44	6	6			12/12 (100%)
40–42	2	2		2	4/6 (67%)

Table 8. Local response according to average minimum tumour temperature

Average minimum tumour temperature (°C)	Local response				
	CR	PRa	PRb	NR	CR+PRa
>42		4			4/4 (100%)
40–42	6	4	1		10/11 (91%)
38–40	2	3		2	5/7 (71%)

Table 9. Local response according to number of effective heat treatments

Number of effective heat treatments†	Local response				
	CR	PRa	PRb	NR	CR+PRa
0–2	1	6		2	7/9 (78%)
3–5	7	6			13/13 (100%)
≥6		6	1		6/7 (86%)

†Effective heat treatment: tumour temperature of >42°C for >20 min.

led to a significantly high local response ($P<0{\cdot}05$). On the other hand, $F_{(>42°C)}$ was under 50% in any heat session for all NR tumours (table 10).

4.5. *Survival rate*

The TNM distribution of primary tumours did not differ significantly between the hyperthermia plus radiotherapy group and radiotherapy-alone group. Therefore survival rates of the patients with primary tumours who did not have a salvage operation were calculated (in each group one patient had a salvage operation after the treatment). Patients treated with thermoradiotherapy survived longer than those treated with radiotherapy alone, although not significantly (figure 1).

4.6. *Toxicity*

Almost all patients complained of pain during heat treatment. Pain sensation was the limiting factor to power elevation. This symptom may be due to overheating of the subcutanenous fat and the edge effect of RF heating. Pain could be eliminated to some

Table 10. Local response according to number of heat sessions whose $F_{(>42°C)}$ was over 50%

Number of heat sessions whose $F_{(>42°C)}$† >50%	Local response				
	CR	PRa	PRb	NR	CR+PRa
0		1		2	1/3 (33%)
≥1	8	10	1		18/19 (95%)

†Sampling fraction of over 42°C.

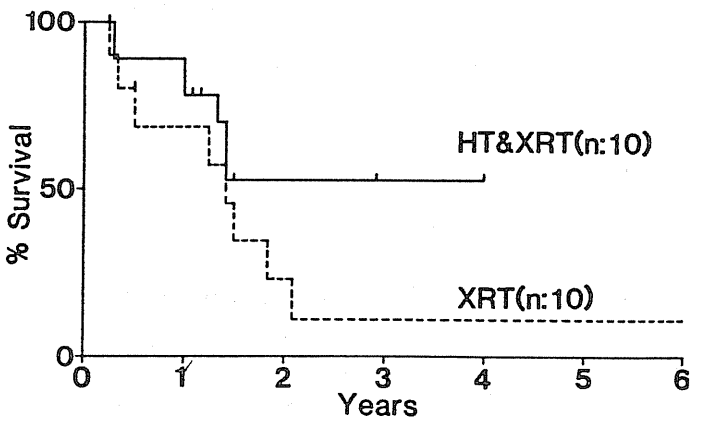

Figure 1. Cumulative survival curves for patients with locally advanced primary tumours treated by thermoradiotherapy or radiotherapy alone (except for the patients undergoing salvage operation).

degree by changing the size or angle of electrodes, fitting large water-pads, or regulating the temperature of perfusing liquid in a surface cooling system. Subacute toxicity signs observed were second-degree skin burn in 10 tumours and moist desquamation in eight tumours. No fat necrosis was observed. As a chronic toxicity an ulcer developed 8 months after treatment in a tumour that had been heavily irradiated.

Complications observed in patients treated with radiotherapy alone were radiation pneumonitis in five patients and radiation dermatitis in five, especially in recurrent tumours after radiotherapy. All these complications, except for radiation pneumonitis in one patient, were relieved with administration of medicine, while the remainder became a major cause of the host's death.

5. Case reports

Case 1 A 49-year-old woman with a primary advanced breast tumour 73 cm^3 in volume was treated with thermoradiotherapy using an 8 MHz capacitive RF. This tumour received a total dose of 74·4 Gy with cobalt-60 gamma-ray in fraction of 1·8 Gy a day, 5 days a week, combined with hyperthermia for 45 min per session, once a week immediately after irradiation, up to a total of eight sessions. $\overline{T_{max}}$, $\overline{T_{min}}$, and $\overline{F_{(>42°C)}}$ were 43·4°C, 40·4°C and 48%, respectively. The local response was CR. This patient is well with no evidence of local recurrence 16 months after treatment (figure 2).

Case 2 A 56-year-old woman with a primary advanced breast tumour 477 cm^3 in volume was treated with thermoradiotherapy using an 8 MHz capacitive RF. Hyperthermia was administered once or twice a week immediately after irradiation for 40 min per session, up to a total of eight sessions. Radiotherapy was delivered in fractions of 2 Gy a day, 5 days a week, up to 64 Gy in total. $\overline{T_{max}}$, $\overline{T_{min}}$, and $\overline{F_{(>42°C)}}$ were 47·3°C, 39·1°C, and 60%, respectively. The local response was PRa. The CT scan taken 8 months after treatment revealed only a calcified area and no apparent tumour in the breast. This patient is well with no evidence of recurrence 13 months after treatment (figure 3).

6. Discussion

There are several rationales in the use of hyperthermia in combination with radiotherapy. (1) The cells in S phase, which are radioresistant, are the most sensitive to hyperthermia. The tumour, which divides more rapidly than normal tissues, is more sensitive than the surrounding normal tissues. (2) The cells that are chronically hypoxic, nutritionally deficient, or in a low pH environment are highly sensitive to hyperthermia. (3) Hyperthermia potentiates the effect of irradiation by interfering with the repair of sublethal damage or potentially lethal damage. (4) Sensitivity of tumours to hyperthermia depends little on histology of the tumours (Hall and Towle 1983, Oleson *et al.* 1984). On the basis of these biological rationales, hyperthermia combined with radiotherapy has been clinically applied for the treatment of many kinds of superficial and deep-seated tumours refractory to radiotherapy (Abe and Hiraoka 1985). Local control rates of locally advanced primary breast tumours by operations are reported to be 40–60% (Bouchaard 1965). Irradiation of over 60 Gy is supposed to leave viable cancer cells in about 75% of locally advanced primary breast tumours (Bouchaard 1965, Golding 1976). There are several reports that local control rates for recurrent breast tumours are higher in thermoradiotherapy than in radiotherapy alone (Kapp *et al.* 1985, Perez *et al.* 1986, Scott *et al.* 1984). In our study the local response rate was fairly good in all groups, except for primary tumours treated by radiotherapy alone. The local control rate in the hyperthermia plus radiotherapy group was comparatively higher than that in radiotherapy-alone group. As we evaluated local response as CR+PRa, these data could not be compared with other researchers' data exactly, but there were few differences between these data and those reported by Kapp *et al.*, Perez

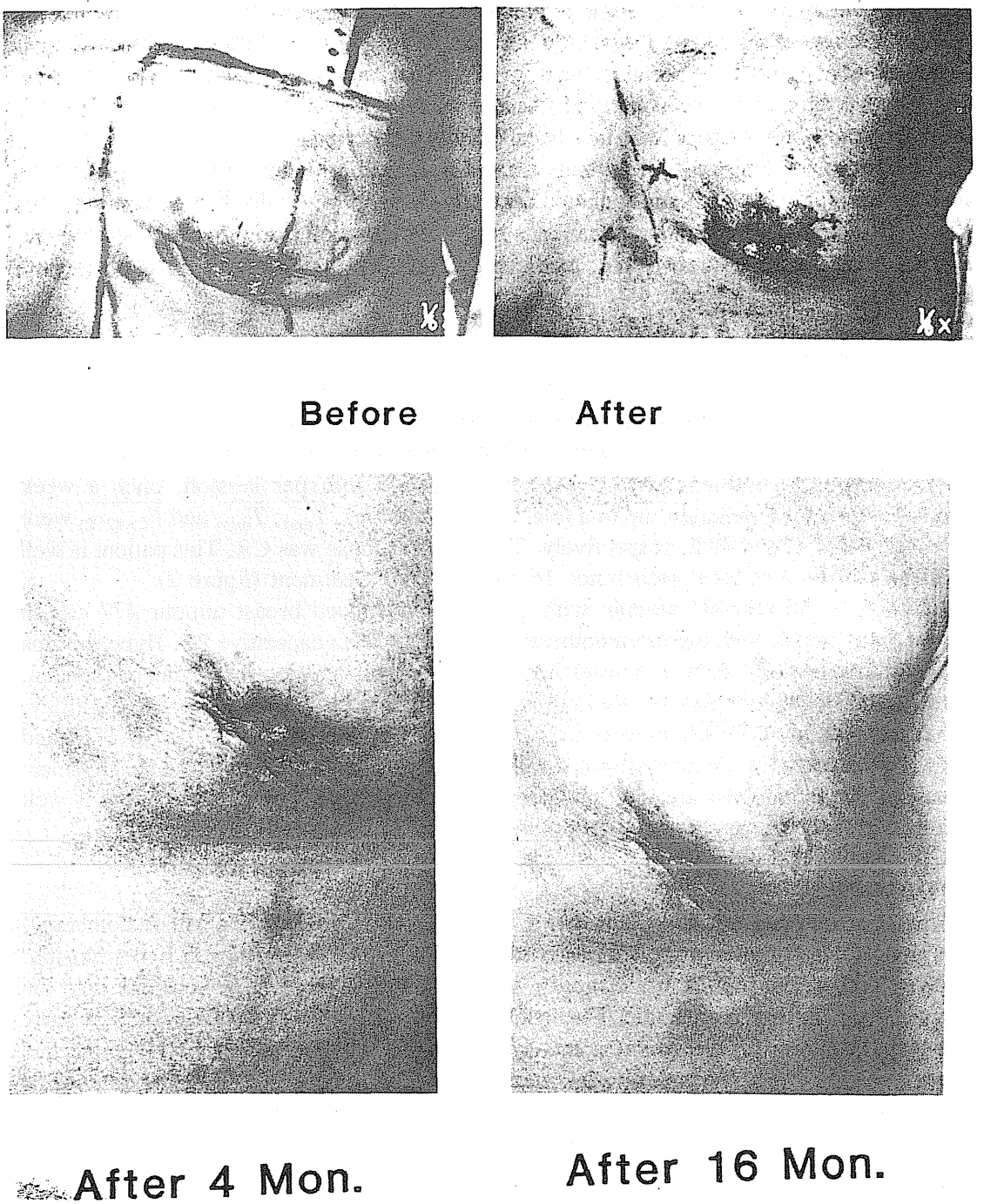

Figure 2. Case report 1 (49-year-old female): (a) pretreatment and post-treatment details of case 1; (b) 4- and 16-month follow-up of case 1.

et al. and Scott *et al.* Thermoradiotherapy seemed to reduce the recurrence or regrowth of locally advanced and recurrent breast tumours (Steeves 1987). Locally advanced primary tumours and recurrent tumours after operation showed an excellent local response to thermoradiotherapy, and this response was likely to be superior to radiotherapy alone. Although the mean TDF of recurrent tumours after radiotherapy in the thermoradiotherapy group was significantly lower than that in the radiotherapy-alone group, the tumour response to thermoradiotherapy was not different from that to radiotherapy. This indicates the

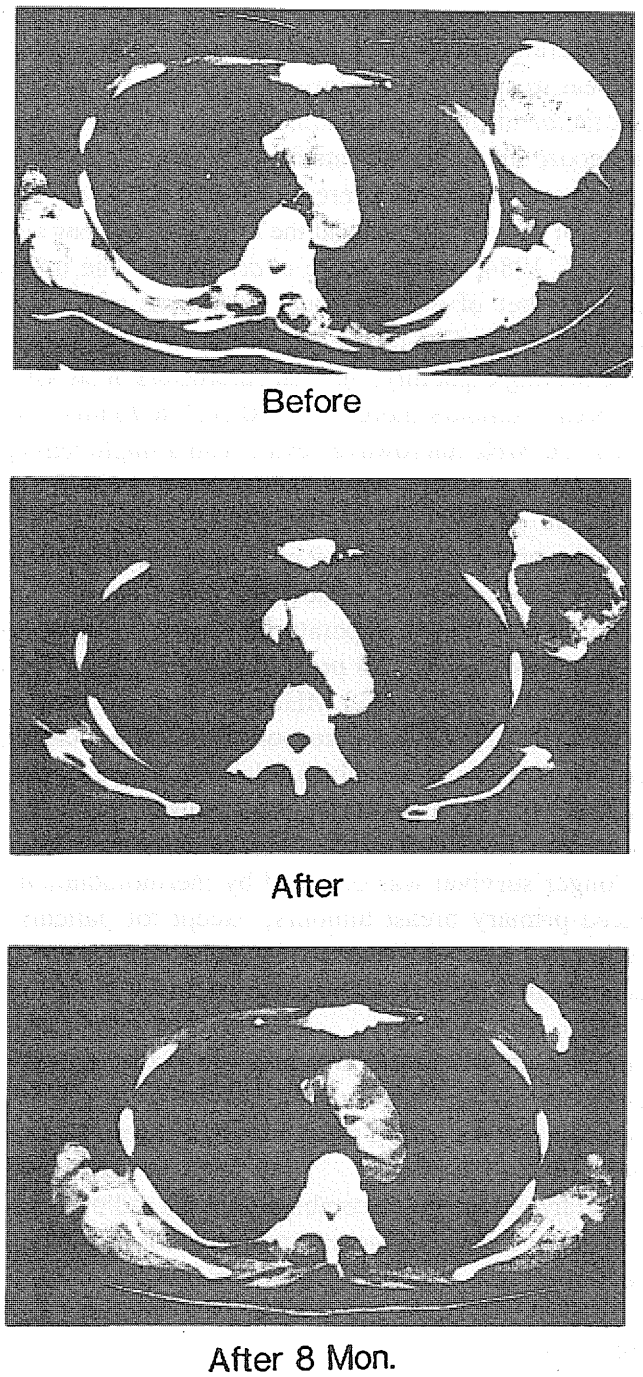

Figure 3. Case report 2 (56-year-old female): pretreatment, post-treatment and 8-month follow-up CT of case 2.

possibility of reducing the total irradiation dose when combined with hyperthermia.

According to the 1986 American Cancer Society statistics on cancer, the estimated number of patients with local failure as a major cause of death made up of 14% of the total number of annual deaths from breast cancer (Kapp 1987). We should regard the local control of breast cancer as important as systemic therapy. Though the number of patients included was too small to draw a conclusion, our results suggest that hyperthermia in combination with radiation therapy is beneficial in the treatment of locally advanced and recurrent breast cancers.

The favourable factors having a tendency to influence the tumour response were average minimum tumour temperature over 40°C, tumour volume smaller than 100 cm^3, more than three effective heat treatments and more than one heat session of which $F_{(>42°C)}$ is over 50%. This last factor influenced the tumour response significantly, and this fact is compatible with the report that obtaining satisfactory heating sessions was more important than the number of heat sessions administered (Oleson *et al.* 1989, Overgaard 1989). The prognostic significance of tumour volume and the minimum tumour temperature is reported elsewhere (Oleson *et al.* 1984, Van der Zee *et al.* 1986). The importance of minimum tumour temperature, number of effective heat treatments and number of good heating sessions indicates the usefulness of hyperthermia as an adjunct of radiation therapy.

With regard to the heating capability, thermal parameters of an RF capacitive equipment were high for large breast tumours more than 100 cm^3 in volume (Abe *et al.* 1986). The heating capability of a 430 MHz microwave device with a single-lens applicator is excellent for localized tumours (Kikuchi *et al.* 1988, Matsuda *et al.* 1988, Nikawa *et al.* 1988). A 2450 MHz microwave device with a multi-applicator can be fairly well applied to superficially spreading tumours (Kawabata *et al.* 1985). However, the thermal profile was inferior to that of a 430 MHz microwave device. According to Oleson's report (Oleson *et al.* 1984), the minimum tumour temperature, which was negatively correlated with tumour volume, was the best variable for predicting CR. $\overline{T_{min}}$ for small localized tumours to which a single-lens applicator of a 430 MHz microwave device could be applied was the highest in our data (table 2), and local responses of these localized tumours were CR or PRa. Apart from large tumours, to which this microwave device cannot be applied, this heating device should be used positively for localized tumours, especially for small recurrent tumours on the chest wall.

Comparatively longer survival was obtained by thermoradiation therapy for patients with locally advanced primary breast tumours, except for patients undergoing salvage operation. On the other hand, survival was not improved for patients with recurrent breast tumours using this combined treatment, possibly due to the frequently coexisting distant metastases.

As shown in our case reports, some tumours, especially large ones, show maximum regression several or more months after thermoradiation therapy. It is necessary to establish the criteria about the time and method of assessing tumour response to thermoradiotherapy (Hiraoka *et al.* 1987).

In conclusion, local hyperthermia in combination with radiotherapy was more effective than radiotherapy alone for locally advanced and recurrent breast cancer, if using heating equipment suitable for various types of breast tumours.

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