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● *Hyperthermia Original Contribution*

CLINICAL EXPERIENCE USING 8 MHZ RADIOFREQUENCY CAPACITIVE HYPERTHERMIA IN COMBINATION WITH RADIOTHERAPY: RESULTS OF A PHASE I/II STUDY

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Purpose: Since 1985, the University of Minnesota Hospital and Clinic has investigated the efficacy and safety of 8 MHz radiofrequency (RF) capacitive hyperthermia using the Thermotron RF-8. This study reports the thermometric and clinical results of 119 patients treated with RF hyperthermia in combination with radiotherapy (RT).

Methods and Materials: Of 119 patients, 69 received high-dose RT and 50 patients received low-dose RT because of previous irradiation to the treatment site. The most common anatomic sites treated were within the pelvic cavity or head and neck area. Thirty-three percent and 24% of tumors treated were > 7 cm and > 10 cm in largest diameter, respectively. Forty percent of the patients had deep-seated tumors (depth > 6 cm). Hyperthermia was given as soon as possible after RT twice weekly, allowing at least 72 h between treatments. The objective was to raise intratumoral temperatures to 42–43°C or above for 30–50 min while keeping normal tissue temperatures below 40–41°C.

Results: Of 119 patients, 40% achieved a T_{max} tumor temperature of > 42°C and 40% achieved 40–42°C T_{max}. Higher T_{max}) tumor temperatures were observed as tumor size increased. Tumors > 10 cm in largest diameter had a T_{max} of 42.2°C. Tumor depth was not a significant factor for the tumor temperatures achieved. Of 119 patients, 11% achieved complete response and 38% achieved partial response. Of the no-response patients, 34% had symptomatic palliation and 15% had stable disease for at least 12 months after treatment. We were able to treat tumors of patients with subcutaneous fat as thick as 3 cm by precooling the fat for 20 min with 10–15°C saline-filled boluses prior to the initiation of heating. During treatment, 60% of patients complained of varying degrees of pain and 19% had pain that was a factor in limiting treatment. Vital signs were relatively stable and not a factor in limiting treatment.

Conclusion: The Thermotron RF-8 is a useful hyperthermia device that can raise tumor temperatures to a therapeutic level (i.e., 42°C) in a significant proportion of patients with superficial, subsurface, and deep-seated tumors, with minimal adverse effects, complications, and systemic stress. Further clinical studies using improved thermometry systems are warranted.

Hyperthermia, Radiotherapy, 8 MHz RF capacitive hyperthermia, Thermotron RF-8.

INTRODUCTION

During the past 2 decades, hyperthermia has evolved steadily as an adjunctive cancer treatment modality that can provide improved local and regional control over radiotherapy and/or chemotherapy alone for some patients. The biological rationale for combining hyperthermia and radiotherapy is well established, and there are widespread reports of improved tumor control using this combined modality for superficial as well as deep-seated tumors (1, 7, 11–13, 21, 28, 33, 35, 43, 44, 52, 54, 57). However, technical difficulties in achieving therapeutic temperatures throughout the tumor, especially with deep-seated tumors, remain to be solved, and clinicians are often constrained by invasive thermometry and poor patient tolerance (4–6, 18, 36).

Investigators in Japan have been using radiofrequency (RF) capacitive devices in the clinical setting since 1979 and have reported impressive results for patients with superficial, as well as large, subsurface, and deep-seated malignancies (1, 16, 17, 29, 53). Although preferential heating of subcutaneous fat tissue has been reported to be a limitation in using RF capacitive heating, the difficulties in treating patients with thick fat have been largely overcome by applying precooling techniques (38).

This report presents the thermometric and clinical re-

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sults of 119 patients treated with 8 MHz RF capacitive hyperthermia using the RF-8[1] in combination with radiotherapy at the University of Minnesota since 1985. Although the RF-8 hyperthermia is used widely in Japan and elsewhere, its use within the United States has been limited. Our objectives are to evaluate the technical capability and safety of the machine, as well as the efficacy of thermoradiotherapy.

METHODS AND MATERIALS

All patients were treated according to a Phase I/II protocol. Patients were informed of the investigational nature of treatment, and informed consent was obtained. Patients eligible for study had to meet the following criteria: (a) measurable tumor was confirmed by physical examination or radiological method. Histological evidence showed either metastatic, recurrent or persistent, inoperable tumor, or tumor known to be resistant to chemotherapy and conventional radiotherapy; (b) conventional treatment was inadequate because of extent of disease, histology, and/or previous irradiation to the treatment site; (c) tumor mass was accessible to allow introduction of temperature probes (thermocouple catheters) without risking complications, such as pneumothorax or bowel damage. [Catheters may be placed under computerized tomography (CT) guidance.]; (d) palliation of symptoms was dependent on tumor response; (e) patient age was greater than 15 years; and (f) minimum life expectancy was greater than 12 weeks. Karnofsky performance status was 50 or greater. Patients may or may not have had distant metastases. Patients ineligible for the study were (a) patients with cardiac pacemakers; (b) patients with large metal prostheses (iron-containing; for example, total joint or rods used for bone fractures); and (c) patients with a tumor mass that is inaccessible to temperature measurement through either an intracavitary or intratumor approach.

Patient Characteristics

A total of 119 patients were treated (60 male and 59 female). Patients were divided into two groups: 69 patients who received standard high-dose radiation therapy (RT) and 50 patients who received low-dose RT (these patients had previous irradiation to the treatment site). The median patient age was 61 years (range 23–87). Median time of follow-up was calculated according to time to stable disease: 11 months for patients with complete response (CR), 6 months for patients with partial response (PR), and 3 months for patients with no response. Patient characteristics were grouped by anatomic site, histopathology, tumor size, tumor depth, thickness of subcutaneous fat, and the radiation dose given (Table 1).

The most commonly treated sites were within the pelvic or head and neck area. Pelvic tumors were the most commonly treated site receiving high-dose RT (26%), whereas head and neck tumors were the most commonly treated site receiving low-dose RT (44%). Adenocarcinoma was the most common histology in the high-dose RT group; in the low-dose RT group, adenocarcinoma and squamous cell carcinoma were the most common histology. Of 119 patients, 81 (68%) had tumors > 5 cm in largest diameter, 42 (35%) had tumors > 7 cm in largest diameter, and 28 (24%) had tumors > 10 cm in largest diameter. There were 45 (38%) patients who had tumors that were superficial, 26 (22%) patients with subsurface tumors (located 3–6 cm in depth), and 48 (40%) patients with deep-seated tumors (> 6 cm in depth). Of the 69 patients who received high-dose RT, 13 (19%) had subsurface tumors and 31 (45%) had deep-seated tumors. In the low-dose RT group, 20 (40%) had superficial tumors and 17 (34%) had deep-seated tumors. Of 119 patients, 37 (31%) had subcutaneous fat thicker than 2 cm over the tumor site.

TREATMENT SCHEMA

Radiotherapy

Patients who had not received previous irradiation to the treatment site received conventional fractionated irradiation (high-dose RT), 1.8–2 Gy per fraction, in addition to hyperthermia treatment. The total dose of radiation delivered was determined according to conventional regimens, for example, by histopathology or tumor size and location. Median radiation dose for patients treated with high-dose radiation was 52 Gy.

Patients who had received previous irradiation to the treatment site were treated with a limited course of radiation as tolerated (low-dose RT), usually 20–30 Gy with 2–3 Gy per fraction. Treatment was given 4–5 days per week for those patients able to receive a cumulative dose of at least 30 or more Gy. Those patients who received low-dose RT were treated twice weekly, on Monday and Thursday, or Tuesday and Friday, in combination with hyperthermia. Median radiation dose for patients treated with low-dose was 26 Gy. All radiation therapy was delivered using a 6, 10, or 18 MeV linear accelerator.

Hyperthermia

The physical features of the RF-8 clinical hypterthermia machine and thermal distribution characteristics in phantom as well as in the human body when heating with this device have been reported previously (15, 22, 48). The size of opposed electrodes for the capacitive heating was determined according to the thickness of the patient at the site, depth, and size of the tumor as reported previously (16, 22, 48). Briefly, for large and deep-seated

[1]Yamamoto Vinyter CO, Osaka, Japan Thernotron.

Table 1. Patient characteristics and radiation dose

Characteristics	Total	RT + Heat	
		High-dose RT	Low-dose RT
	No. pts (%)*	No. pts (%)*	No. pts (%)*
All	119 (100)	69 (100)	50 (100)
Anatomic sites			
Head and neck	34 (29)	12 (17)	22 (44)
Thorax	11 (9)	4 (6)	7 (14)
Chest wall	22 (18)	15 (22)	7 (14)
Abdomen	8 (7)	6 (9)	2 (4)
Pelvic cavity	27 (23)	18 (26)	9 (18)
Outside of pelvis	5 (4)	3 (4)	2 (4)
Extremities	12 (10)	11 (16)	1 (2)
Histopathology			
Squamous cell carcinoma	30 (25)	13 (19)	17 (34)
Adenocarcinoma	48 (40)	29 (42)	19 (38)
Soft tissue sarcoma	14 (12)	9 (13)	5 (10)
Melanoma	10 (8)	17 (10)	3 (6)
Others	17 (14)	11 (16)	6 (12)
Tumor size†			
< 3 cm	6 (5)	1 (1)	5 (10)
3–5 cm	32 (27)	17 (25)	15 (30)
5–7 cm	39 (33)	28 (41)	11 (22)
7–10	14 (12)	4 (6)	10 (20)
≥ 10 cm	28 (24)	19 (28)	9 (18)
Tumor depth			
Superficial	45 (38)	25 (36)	20 (40)
Subsurface	26 (22)	13 (19)	13 (26)
Deep	48 (40)	31 (45)	17 (34)
Fat thickness			
< 1 cm	39 (33)	15 (22)	24 (48)
1–2 cm	43 (36)	27 (39)	16 (32)
2–3 cm	30 (25)	21 (30)	9 (18)
≥ 3 cm	7 (14)	6 (9)	1 (2)

RT = Radiotherapy.
* Percent of patients per category of radiation dose.
† Largest diameter.

tumors, a pair of large electrodes was used. For superficial lesions, a small electrode was coupled to the lesions, opposing a larger electrode.

Hyperthermia was given as soon as possible after RT twice weekly, usually on Monday and Thursday, or Tuesday and Friday, allowing at least 72 h between treatments. Heating duration was 30–50 min after the intratumoral temperatures reached a plateau, which usually occurred 5–15 min after heating began. For patients with widespread lesions, such as chest wall recurrences from breast cancer, the treatment field was divided into two to four sections, and heated sequentially for 30–50 min/section twice per week.

To improve the coupling of electrodes to the body and to reduce heat-related discomfort at the edge of the electrodes, saline-filled boluses were attached in front of the metal electrodes. Temperatures of the saline boluses were determined by the depth and location of the treatment site and were controlled independently by circulating the saline through separate heat exchangers. For patients with subcutaneous fat tissue > 2 cm in thickness, superficial tissue was cooled for 15–20 min prior to and during heating with 10–15°C saline (37). For heating deep areas of the body, an overlay bolus sheet in addition to the regular bolus was applied and the body surface was cooled continuously during heating.

The objective was to raise intratumoral temperatures to 42°C or above for at least 30 min while keeping normal tissue temperatures below 41°C.

Thermometry

Temperatures were measured with the use of thin Teflon-coated copper-constantan microthermo-couples,[2] which were placed into the treatment site through plastic

[2]Type IT-18, Sensortek, Inc., NJ.

catheters. For superficial and subsurface tumors that were palpable or presented no danger of blind organ puncture in accessing 16–21 gauge catheters, angiocatheters were placed before each treatment. The skin was cleansed with betadine solution and a small amount of local anesthetic injected at the site. Because the tumor heating was initiated 15–20 min after an injection of anesthetic and the injected superficial area was cooled during the tumor heating, minimal thermosensitization due to the anesthetic was expected. Catheters[3] were placed into the tumor, the stylet removed, and microthermocouples inserted into the hollow catheter. The thermocouples were connected to the computerized thermometry system, which is built into the RF-8, and tumor temperatures were recorded each minute. The temperatures were also displayed visually during heating and printed after heating.

The RF-8 is equipped with four thermometry channels, limiting thermometry to four sites. Attempts were made to place three thermocouples into the tumor tissue and one thermocouple into surrounding normal tissues (usually within subcutaneous fat tissue). In many cases, however, only one or two catheters could be placed into the tumor because of the location and depth of the tumor. In some cases, three-junction thermocouples were used to measure temperatures at three different points 1 cm apart along a catheter axis. If possible, a pull-back technique was used with both single- and three-junction thermocouples, pulling back the thermocouple at 1 cm intervals to measure the temperatures achieved along the tract of the catheter. Such temperature mapping was done only occasionally to minimize both interruptions during treatment and patient discomfort and anxiety.

For patients whose tumor mass was inaccessible to safe insertion of computerized tomography-guided catheter placement, we placed intracavitary probes within the organ cavities, such as bladder, rectum, and vagina; when located within the treatment field, the cavitary temperature of the area adjacent to the tumor mass was measured. On the average, the number of temperature probes per treatment were two in the tumor and two in the normal tissues. In most cases, each probe measured one point per thermocouple.

Thermal Parameters

Thermal profiles were analyzed by obtaining $T_{\overline{max}}$, $T_{\overline{ave}}$, and $T_{\overline{min}}$, which were modified from the terminology of the Hyperthermia Equipment Evaluation Contractors' Group (NCI) (20). $T_{\overline{max}}$ and $T_{\overline{min}}$ were the average of the single highest and lowest temperatures, respectively, recorded within the treatment volume during individual sessions, and $T_{\overline{ave}}$ was the average of the mean of all temperatures measured during individual sessions, after temperatures reached a plateau. For example, if a patient received 10 hyperthermia treatments, $T_{\overline{max}}$ was an average of 10 values, each of which represented the highest intratumoral temperature measured during an individual treatment. Likewise, $T_{\overline{ave}}$ represented an average of 10 values, each of which represented a mean of all measured intratumoral temperatures, and $T_{\overline{min}}$ was an average of 10 values, each of which represented the lowest intratumoral temperatures measured during individual heat treatments. Intratumoral temperature parameters, $T_{\overline{max}}$, $T_{\overline{ave}}$, and $T_{\overline{min}}$, were analyzed according to percentage of temperatures reaching < 40°C, 40–<42°C, and ≥ 42°C.

Other thermal parameters used were $t_{\overline{rise}}$, and $t_{\overline{dur}}$; $t_{\overline{rise}}$, which was the average time to reach plateau temperature from the start of heating, and $t_{\overline{dur}}$, which was the average duration of heating after the temperatures reached a plateau.

Statistical Analysis

Thermal parameters were analyzed according to patient characteristics. The students' *t*-test was used to determine the significance of differences among various subgroups of patient characteristics.

Evaluation of Toxicity

Blood pressure, pulse, and systemic temperature were monitored at 10–15-min intervals prior to, during, and after heat treatments. Any complications resulting from previous heat treatments were evaluated before subsequent treatments. All patients were evaluated at 1, 2, and 3 months after thermoradiotherapy, and then every 2 to 3 months for patients who were able to come to the clinic.

RESULTS

Temperature Profiles

An average of 7.2 thermal treatments (range 3–10) were applied per patient, and a total of 859 temperature measurements were obtained among 119 patients.

The treatment duration averaged 40 min and the $t_{\overline{rise}}$ averaged about 10 min; $t_{\overline{rise}}$ was slightly longer for deep-seated tumors compared to that for superficial or subsurface tumors. It was not always possible to achieve therapeutic intratumoral temperatures (i.e., above 42°C).

The relationship among various patient characteristics and the means of $T_{\overline{max}}$, $T_{\overline{ave}}$, and $T_{\overline{min}}$ are shown in Table 2. The mean $T_{\overline{max}}$ of normal tissue was 37.8° and 41.4°C for tumors. The mean $T_{\overline{ave}}$ and $T_{\overline{min}}$ of tumor were 40.7° and 39.3°C, respectively. The highest mean $T_{\overline{max}}$ and $T_{\overline{ave}}$ were observed in the tumors of extremities, while the lowest mean $T_{\overline{max}}$ and $T_{\overline{ave}}$ were observed in the tumors of pelvis. These differences in the thermal pattern between the tumors in pelvis and extremities were statistically different ($p < 0.05$). The mean $T_{\overline{max}}$ and $T_{\overline{ave}}$ of melanoma and soft tissue sarcoma were slightly higher

[3]Angiocath or Deseret Teflon.

Table 2. Mean of $T_{\overline{max}}$, $T_{\overline{ave}}$, $T_{\overline{min}}$

Characteristics	No. pts	Normal tissues (°C) $T_{\overline{max}}$	Tumor tissues (°C) $T_{\overline{max}}$	$T_{\overline{ave}}$	$T_{\overline{min}}$	Tstd
All	119	37.8	41.4	40.7	39.3	0.50
Anatomic sites						
Head and neck	34	36.2	41.2	40.6	39.2	0.49
Thorax	11	38.2	41.2	40.2	39.6	0.56
Chest wall	22	39.2	41.9	41.1	39.0	0.53
Abdomen	8	37.4	41.4	40.8	40.7	0.49
Pelvic cavity	27	39.3	40.5	40.1	39.4	0.41
Outside pelvis	5	36.9	42.3	41.6	37.3	0.51
Extremities	12	36.7	42.9	42.1	39.7	0.60
Histopathology						
Squamous cell carcinoma	30	37.0	41.3	40.5	39.7	0.47
Adenocarcinoma	48	38.8	41.3	40.8	39.1	0.47
Soft tissue sarcoma	14	36.4	41.9	41.2	39.3	0.51
Melanoma	10	37.6	42.1	41.2	38.7	0.55
Others	17	38.0	40.8	40.3	39.3	0.59
Tumor size						
1–3 cm	6	37.2	39.7	39.6	39.1	0.40
3–5 cm	32	38.4	41.1	40.5	39.0	0.46
5–7 cm	39	36.8	41.3	40.6	38.8	0.53
7–10 cm	14	39.3	41.8	41.2	40.1	0.42
≥ 10 cm	28	37.9	42.2	41.4	39.8	0.56
Tumor depth						
Superficial	45	36.5	41.8	40.9	38.7	0.55
Subsurface	26	38.8	41.0	40.6	39.3	0.46
Deep	48	38.4	41.3	40.7	40.3	0.47
Fat thickness						
< 1 cm	39	36.4	41.1	40.5	39.3	0.51
1–2 cm	43	38.3	42.1	41.3	39.4	0.49
2–3 cm	30	38.9	40.9	40.3	38.7	0.51
≥ 3 cm	7	38.8	41.2	40.7	39.9	0.43

than those in others, although the differences were not statistically significant. The average $T_{\overline{max}}$, $T_{\overline{ave}}$, and $T_{\overline{min}}$ were not significantly associated with size and depth of tumors or with fat thickness. The percentage distribution of temperature for different patient characteristics are illustrated in Figs. 1–4.

Overall, a $T_{\overline{max}}$ of ≥ 42°C and $T_{\overline{ave}}$ of ≥ 42°C were achieved in 40 and 25% of all patients, respectively. A $T_{\overline{min}}$ of ≥ 42°C was observed in 9% of patients. By anatomic site (Fig. 1), the highest proportion of patients who had $T_{\overline{max}}$ ≥ 42°C were those with chest wall (61%) and extremity lesions (64%). By histopathology, the highest $T_{\overline{max}}$ and $T_{\overline{ave}}$ were obtained in those with soft tissue sarcoma, with $T_{\overline{max}}$ ≥ 42°C in 49% and $T_{\overline{ave}}$ ≥ 42°C in 34% of the tumors. Among patients with melanoma, 44% had $T_{\overline{max}}$ ≥ 42°C and 32% had $T_{\overline{ave}}$ > 42°C. $T_{\overline{max}}$ ≥ 42°C was obtained in 29% of tumors < 5 cm in largest diameter and 50% of tumors > 7 cm in largest diameter (Fig. 2). Similarly, $T_{\overline{ave}}$ ≥ 42°C was observed in 15% and 37% of tumors having < 5 cm and > 7 cm in largest diameter, respectively. Temperatures measured in the superficial and subsurface tumors tended to be higher compared to those in the deep-seated tumors (Fig. 3). However, the only statistically significant difference noted was between the $T_{\overline{max}}$ in the superficial and deep-seated tumors. Temperature distribution in tumors also varied depending on the thickness of subcutaneous fat (Fig. 4). Whereas $T_{\overline{max}}$ ≥ 42°C was achieved in 49% of patients with a 1–2 cm thick fat layer, it was achieved in only 34% of patients with a thicker fat layer.

Clinical Response

Patients were examined at follow-up monthly intervals for 1, 2, and 3 months after completion of therapy, then every 2–3 months if possible. The tumor response observed within 1–2 months after treatment was categorized according to (a) complete response (CR), or complete regression of all clinically detectable disease; (b) partial response (PR), or ≥ 50% reduction in tumor diameter; and (c) no response (NR), or ≤ 50% reduction in tumor diameter.

Tumor response (CR, PR, NR), palliation of symptoms, and duration of stable disease are shown in Table 3. Of 119 patients, 13% achieved CR and 36% PR, for a total response rate of 49%. Palliation of symptoms was observed in 30 and 34% of the PR and NR groups, respectively. Median follow-up was 12 months (range 1–60 months).

Tumor response by patient characteristics and RT dose evaluated 3 months after treatment by physical and/or

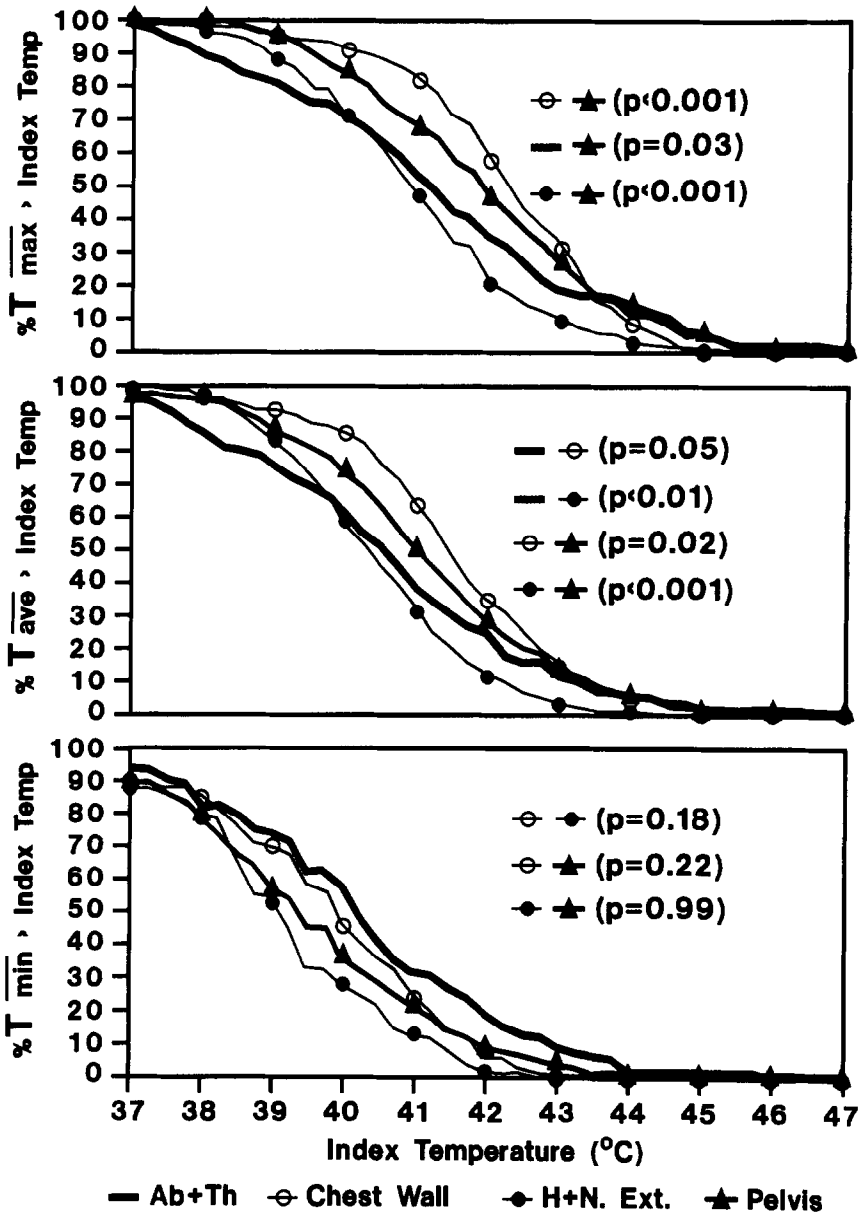

Fig. 1. Graphic comparison of thermal profiles (defined by $T_{\overline{max}}$, $T_{\overline{ave}}$, $T_{\overline{min}}$) according to anatomic site.

radiographic methods is shown in Table 4. Of 69 patients who received high-dose RT in combination with hyperthermia, 11 patients (16%) achieved CR, 25 patients (36%) achieved PR, and 33 patients (48%) had NR. Of 50 patients who received low-dose RT in combination with hyperthermia, 4 patients (8%) achieved CR, 18 patients (36%) achieved PR, and 28 patients (56%) had NR. The overall response rate (CR + PR) for the high-dose RT group was 52%, and 44% for the low-dose RT group.

Tumor response related to RT dose and temperature parameters ($T_{\overline{max}}$ and $T_{\overline{ave}}$) is shown in Tables 5 and 6. Table 5 shows that the response rate (CR + PR) in the high-dose RT group correlates with $T_{\overline{max}}$, with a response rate of 63% (23% CR + 40% PR) in patients with $T_{\overline{max}}$ of $\geq$ 42°C, 53% (9% CR + 44% PR) in patients with $T_{\overline{max}}$ of 40 to < 42°C, and 32% (13% CR + 19% PR) in patients with $T_{\overline{max}}$ of < 40°C. This increase in treatment response with increase in temperature was significant ($p < 0.05$). For patients treated with low-dose RT, the response rate between patients treated with $T_{\overline{max}}$ of $\geq$ 42°C vs. patients treated at lower temperatures was significant ($p < 0.05$) (Table 5). For high-dose RT and $T_{\overline{ave}}$, a moderate correlation was found between the increase in temperature and increase in treatment response (Table 6); no correlation was found between low-dose RT and $T_{\overline{ave}}$.

Survival

Of 15 patients who achieved CR, 20% (3 of 15) died of disease in the treated area at 7, 16, and 26 months, whereas 40% (6 of 15) died of metastasis at a median time of 5 months. Another 20% (3 of 15) died without active disease: one patient from a cerebrovascular accident at 60 months and two from hemorrhage at 2 months after treatment. Two of the 15 (CR) patients are alive

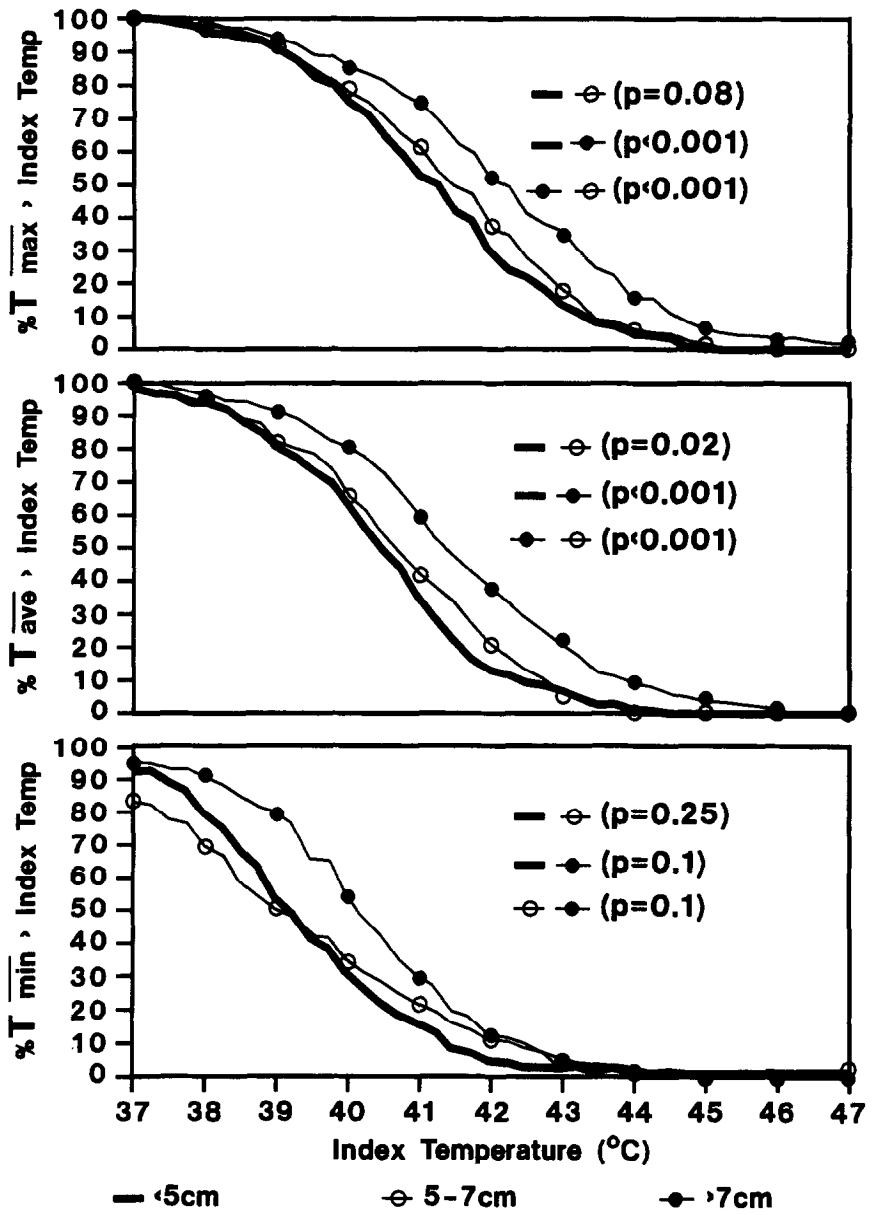

Fig. 2. Graphic comparison of thermal profiles (defined by $T_{\overline{max}}$, $T_{\overline{ave}}$, $T_{\overline{min}}$) according to tumor size.

without disease at 3 and 60 months, and one is alive with disease at 36 months.

Among 43 patients who achieved PR, 40% (17 of 43) died due to disease in the treated area in 1–54 months (median 4 months); 44% (19 of 43) died of metastasis, and 7% (3 of 43) died from other causes. One patient in the PR group who underwent tumor resection after thermoradiotherapy is alive without disease at 59 months. Three of the PR patients are alive with stable disease at 32, 50, and 55 months.

Of 61 patients who had NR, 48% (29 of 61) died due to disease in the treated area, and 34% (21 of 61) died from metastasis. Seven of these NR patients are alive: two patients without disease following postthermoradiotherapy surgery, and five patients with disease at a median follow-up of 41 months. Survival curves of these patients were not evaluated because they were treated for palliation and were poor risk patients.

Adverse Effects

Blood pressure, pulse, and core body temperatures did not change significantly and were not a limiting factor in treatment. Overall, approximately 6% of patients had pulse rate or systolic blood pressure changes of more than 20. When large electrodes were used to heat deep-seated and/or larger tumors, the majority of patients experienced sweating and a generalized warm sensation during heating. After treatment, patients often experienced fatigue for a day or two. Skin within the treatment area often became erythematous for 1–2 h following treatment, but did not appear to exacerbate skin damage from irradiation.

The most common patient complaint during heating

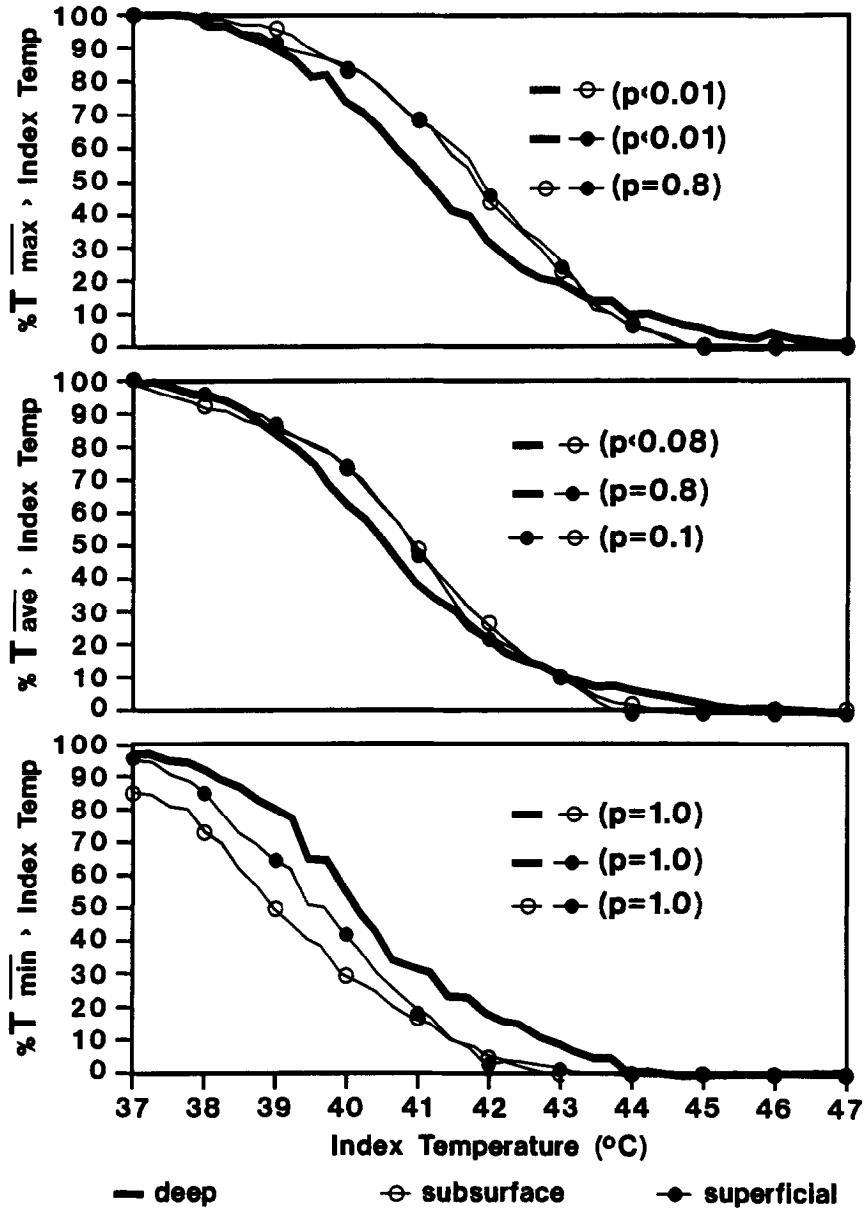

Fig. 3. Graphic comparison of thermal profiles (defined by $T_{\overline{max}}$, $T_{\overline{ave}}$, $T_{\overline{min}}$) according to tumor depth.

was pain and/or the sensation of a hot spot; 60% of patients complained of varying degrees of pain, and 19% had pain severe enough to reduce the RF power applied. Complaints of hot spot were more frequent during the treatment of superficial lesions. Pain often occurred near the edge of the electrode(s), at the site of the catheter, or when heat was applied near bony areas. Pain near the electrode edge could often be reduced by using a blanket-shaped overlay bolus in addition to the regular bolus to minimize contact between the electrode edge and body surface. Patient discomfort was often greater when the treatment site was covered with a thicker layer of subcutaneous fat (> 2 cm). Pain could be reduced by using a precooling technique as described previously. Other adverse effects included blisters (16% of patients), infection (1% of patients), bleeding (3% of patients), and fat necrosis (3% of patients).

Temperatures in scar tissue rose higher than that in surrounding normal tissues during heating. One patient developed an open wound at the surgical scar site resulting from fat tissue necrosis. Late side effects were not significantly different, other than fibrosis, and seemed dependent on total dose of radiation, including previous treatment and extent of disease.

DISCUSSION

Our objectives in this Phase I/II study were to assess patient tolerance, temperature profiles, toxicity, adverse effects, and the subjective and objective benefits of hyperthermia treatment using a RF-8. Of 119 patients, 49% achieved a response (11% CR and 38% PR). Approximately one-third of the PR and NR patients had symptomatic palliation following treatment. Treatments were

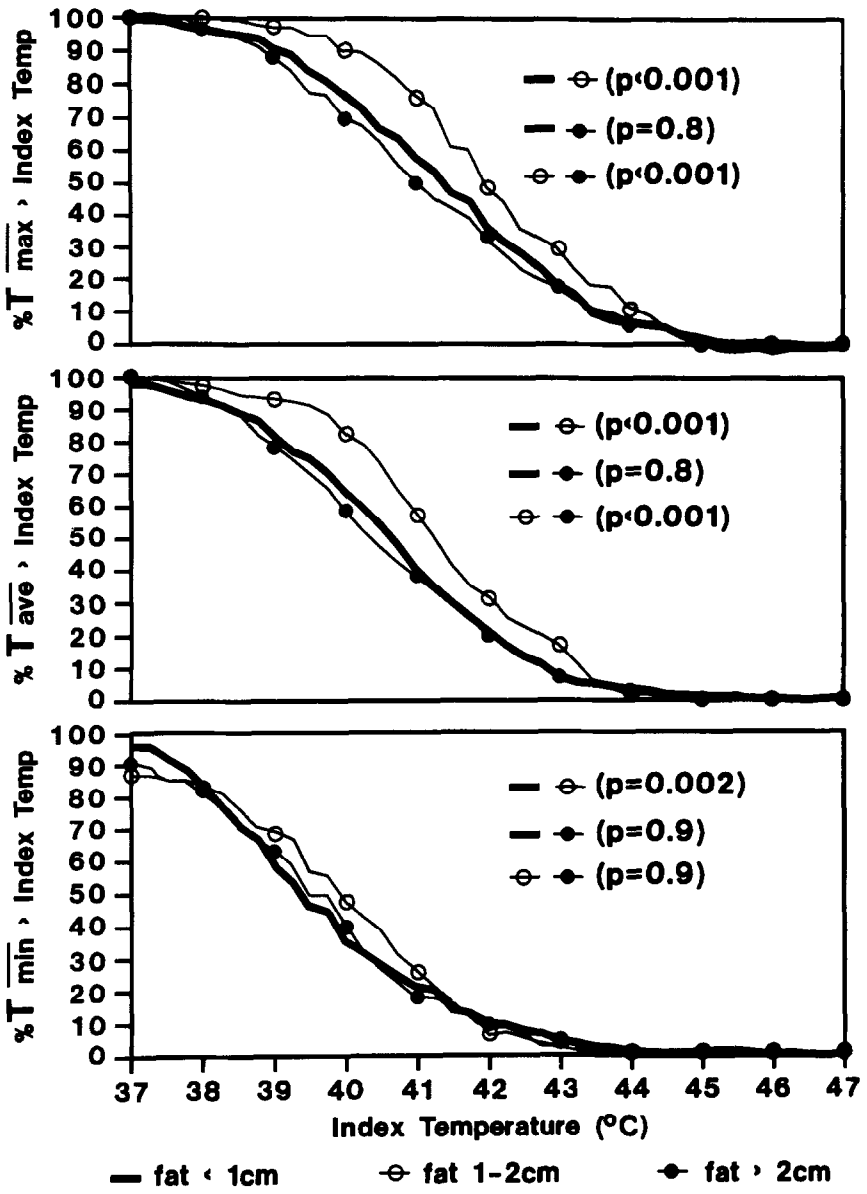

Fig. 4. Graphic comparison of thermal profiles (defined by $T_{\overline{max}}$, $T_{\overline{ave}}$, $T_{\overline{min}}$) according to fat thickness.

well tolerated by the majority of patients, although 19% of the 119 patients treated had pain during heating significant enough that applied power had to be reduced in at least one heat session during the course of multiple heat treatments. There was no adverse systemic effect. The local adverse effects were mostly transient in nature and resolved without difficulty. The most serious inherent problem with RF capacitive heating is the preferential heating of subcutaneous fat. This difficulty was minimized with vigorous cooling, enabling treatment of pa-

Table 3. Tumor response

Response	CR	PR	NR
No. of patients	15	43	61
Palliation of symptoms	15 (100%)	13/43 (30%)	21/61 (34%)
Median time of stable disease	11 M (3–61 M)	6 M (1–48 M)	3 M (1–60 M)
No. of patients with stable disease ≥ 12 M	8/15 (53%)	14/43 (33%)	9/61 (15%)

CR = Complete response.
PR = Partial response.
NR = No response.

Table 4. Tumor response as related to radiation dose and patient characteristics

	High dose RT + heat				Low dose RT + heat			
		CR	PR	NR		CR	PR	NR
Characteristics	Total	No. (%)*	No. (%)	No. (%)	Total	No. (%)	No. (%)	No. (%)
All patients	69	11 (16)	25 (36)	33 (48)	50	4 (8)	18 (36)	28 (56)
Anatomic sites								
Head and neck	12	0 (0)	8 (67)	4 (33)	22	1 (5)	12 (55)	9 (41)
Thorax	4	1 (25)	0 (0)	3 (75)	7	0 (0)	0 (0)	7 (100)
Chest wall	15	5 (33)	5 (33)	5 (33)	7	2 (29)	3 (43)	2 (29)
Abdomen	6	0 (0)	2 (33)	4 (67)	2	0 (0)	1 (50)	1 (50)
Pelvic cavity	18	3 (17)	5 (28)	10 (56)	9	0 (0)	1 (11)	8 (89)
Outside of pelvis	3	2 (67)	0 (0)	1 (33)	2	1 (50)	1 (50)	0 (0)
Extremities	11	0 (0)	5 (46)	6 (55)	1	0 (0)	10 (0)	1 (100)
Histopathology								
Squamous cell carcinoma	13	1 (8)	9 (69)	3 (23)	17	1 (6)	7 (41)	9 (53)
Adenocarcinoma	29	5 (17)	8 (28)	16 (55)	19	2 (11)	7 (37)	10 (53)
Soft tissue sarcoma	9	1 (11)	2 (22)	6 (67)	5	0 (0)	1 (20)	4 (80)
Melanoma	7	3 (43)	3 (43)	1 (14)	3	0 (0)	1 (33)	2 (67)
Others	11	1 (9)	3 (27)	7 (64)	6	1 (17)	2 (33)	3 (50)
Tumor size								
< 3 cm	1	0 (0)	0 (0)	1 (100)	5	1 (20)	1 (20)	3 (60)
3–5 cm	17	5 (29)	6 (35)	6 (35)	15	1 (7)	8 (53)	6 (40)
5–7 cm	28	4 (14)	15 (54)	9 (32)	11	0 (0)	4 (36)	7 (64)
7–10 cm	4	0 (0)	1 (25)	3 (75)	10	0 (0)	4 (40)	6 (60)
≥ 10 cm	19	2 (11)	3 (16)	14 (74)	9	2† (22)	1 (11)	6 (67)
Tumor depth								
Superficial (0–3 cm)	25	5 (20)	11 (44)	9 (36)	20	0 (0)	10 (50)	10 (50)
Subsurface (3–6 cm)	13	3 (23)	5 (39)	5 (39)	13	4 (31)	5 (39)	14 (31)
Deep (≥ 6 cm)	31	3 (10)	9 (29)	19 (61)	17	0 (0)	3 (18)	14 (82)

CR—complete response, complete regression of tumor volume; PR—partial response, ≥ 50% regression of tumor volume; NR—no response, < 50% regression of tumor volume.
* (%) = percentage of total number of patients by patient category and radiation dose.
† = one postoperative patient.

tients with 2–3 cm thick fat layers. There were no significant differences in temperature profiles in tumors of different histopathology, anatomic site, or size. Although some investigators have found no correlation between tumor response and temperatures achieved (30, 37, 56, 57), we found a linear correlation between treatment response and temperatures achieved in a patients treated with high-dose RT (i.e., treatment response increased as temperature increased). Other recent studies also show a relationship between temperature distribution and tumor response (26).

Inadequate thermometry and the analysis of temperature data remain our greatest challenge in using the RF-8. Thermometry is most limited with regional heating and deep heating, such as for tumors located within the pelvis. Obtaining a measurement of temperatures within deep

Table 5. Tumor response as related to $T_{\overline{max}}$ and radiation dose

	$T_{\overline{max}}$ < 40°C	$T_{\overline{max}}$ 40 – < 42°C	$T_{\overline{max}}$ ≥ 42°	Total
Radiation dose	No. pts (%)*	No. pts (%)	No. pts (%)	No. pts (%)
High dose RT	16 (100)	23 (100)	30 (100)	69 (100)
Complete regression	2 (13)	2 (9)	7 (23)	11 (16)
Partial regression	3 (19)	10 (44)	12 (40)	25 (36)
No regression	11 (69)	11 (48)	11 (37)	33 (48)
Low dose RT	7 (100)	21 (100)	22 (100)	50 (100)
Complete regression	0 (0)	2 (10)	2 (9)	4 (8)
Partial regression	3 (43)	4 (19)	11 (50)	18 (36)
No regression	4 (57)	15 (71)	9 (41)	28 (56)

* (%) percent of patients by category.
RT = Radiotherapy.

Table 6. Tumor response according to $T_{\overline{ave}}$ and radiation dose

Radiation dose	$T_{\overline{ave}} < 40°C$ No. pts (%)*	$T_{\overline{ave}}$ 40 – < 42°C No. pts (%)	$T_{\overline{ave}} \geq 42°$ No. pts (%)	Total No. pts (%)
High dose RT	25 (100)	30 (100)	14 (100)	69 (100)
Complete regression	3 (12)	5 (18)	3 (21)	11 (16)
Partial regression	9 (36)	11 (37)	5 (36)	25 (36)
No regression	13 (52)	14 (47)	6 (43)	33 (48)
Low dose RT	10 (100)	32 (100)	8 (100)	50 (100)
Complete regression	2 (20)	1 (3)	1 (13)	4 (8)
Partial regression	3 (30)	12 (38)	3 (38)	18 (36)
No regression	5 (50)	19 (59)	4 (50)	28 (56)

* (%) percent of patients by category.
RT = Radiotherapy.

tumors sometimes requires measuring the temperatures within adjacent cavities, such as the rectum or vagina. Temperatures measured along one or two catheter tracks may not characterize temperatures attained within the entire tumor volume.

Invasive thermometry may also contribute to patient discomfort and anxiety, a factor that limited our use of thermal mapping because of the increased patient discomfort associated with interrupting treatment to measure temperatures along the track of the catheter. Although adverse effects of deep heating have not been greater than with superficial heating, poor patient tolerance and compliance are significant factors that have limited deep or regional heating (23, 25, 36, 40, 41, 51). To minimize patient discomfort and allow one to reach goal temperatures, the clinician may find it necessary to limit thermometry.

Despite these difficulties, a number of reports indicate significantly better results with thermoradiotherapy compared to standard radiotherapy using a variety of hyperthermia devices, especially for patients with superficial and subsurface malignancies (2, 8, 9, 14, 19, 21, 27, 32, 39, 45–47, 51, 55). In a recent multiinstitutional study of the effects of hyperthermia on deep-seated lesions, 53 patients received either microwave or radiofrequency hyperthermia treatment in addition to RT (10). Complete response and partial response were observed in 39 and 14% of the patients, respectively. In the United States, most clinical studies on hyperthermia for bulky or deep-seated tumors have been carried out using microwave or ultrasound devices. In Japan, a number of investigators have reported considerable experience and success using RF capacitive devices for large and deep-seated tumors, as well as superficial and subsurface tumors (1, 16, 17, 29, 37a).

It is difficult to compare the temperature profiles and clinical results achieved at various institutions, given the wide variety of devices and approaches, as well as differences in patient populations. Our overall response rates were not as favorable as those reported by Japanese investigators, especially for deep-seated tumors (16). This may be due, in part, to differences in patient populations. Deep or regional heating with 8 MHz RF capacitive devices is more easily achieved in patients with smaller frames and less subcutaneous fat, as is seen in the Japanese population. Patient groups may also vary in terms of overall survival status and whether thermoradiotherapy is applied early in the treatment process rather than after other treatment modalities have failed.

Hyperthermia combined with irradiation has been shown to have a profound therapeutic advantage, both in terms of initial response and persistence of response over radiotherapy alone (3–5, 27). An evaluation of clinical response is commonly based on tumor regression, defined by CR, PR, or NR. Stable disease after hyperthermia treatment is also an important criteria of tumor response, not only because most of these patients have significant palliation and subjective improvement, but also because many tumors that fail to regress and are subsequently resected are found to contain no viable cancer cells (4, 16, 17, 28, 42, 50). We observed that thermoradiotherapy may also provide benefits for patients who do not achieve tumor regression. Of the 61 NR patients within the present study, 34% had palliation and 15% had stable disease for at least 12 months after treatment.

Hyperthermia has evolved as a safe and effective adjunctive treatment modality for cancer patients who require more than the effects of surgery, radiation, or chemotherapy alone. It allows the clinician to selectively deliver an additional cell killing and radiosensitizing therapy to malignant lesions. Despite the technical limitations that exist with currently available devices, hyperthermia has been shown to provide significant curative and palliative benefits in combination with RT. Although the great majority of hyperthermia patients are treated for previous treatment failure or metastatic disease, its clinical use and integration into the practice of oncology has become well established and will undoubtedly continue to develop (20, 30, 31, 34, 49, 53, 55). Because of significant technological advances being made in hyperthermia delivery and thermometry systems in addition to widespread research and clinical efforts worldwide, we anticipate that hyperthermia will become more quantitatively achievable and available to a greater number of cancer patients.

CONCLUSION

This study has demonstrated that a RF-8 is a safe and effective hyperthermia system, which can be used for heating superficial, subsurface, and deep-seated tumors with good patient tolerance and relatively few adverse effects and complications. Further clinical study using a RF8 is warranted, with efforts toward improved thermometry and greater documentation of tumor temperatures. A site-specific analysis of temperature profiles and tumor response is forthcoming.

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