# Development of RF and Microwave Heating Equipment and Clinical Applications to Cancer Treatment in Japan

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***Abstract*—Development of RF and microwave (MW) heating equipment for hyperthermia and their clinical applications to various cancers undertaken in Japan have been reviewed in this paper. Originally developed heating devices include an RF capacitive and RF inductive heating device, an MW heating device with a lens applicator, an RF intraluminal heating device, an RF current interstitial heating device, and a ferromagnetic implant heating device. The concept and characteristics of those devices are described herein. Nonrandomized and randomized trials undertaken for superficial and deep-seated tumors demonstrated improved local response with the combined use of hyperthermia. Furthermore, the complications associated with treatment were not generally serious, except for chronic bowel damages suggested in a trial for colorectal cancers. These clinical results indicate the benefit of combined treatment of hyperthermia and radiotherapy. With the advancement of heating and thermometry technologies, hyperthermia will be more widely and safely used in the treatment of cancers.**

***Index Terms*—Capacitive heating, clinical trial, hyperthermia, inductive heating, intaluminal heating, interstitial heating.**

## I. Introduction

DURING THE past two decades, hyperthermia in combination with radiotherapy or chemotherapy has been investigated basically and clinically as a new cancer treatment modality. Numerous biological experiments demonstrate strong biological rationale for the use of hyperthermia in cancer therapy [1], [2].

Problems related to the physics and engineering of hyperthermia have also been investigated. Many kinds of heating techniques and methods for accurately measuring temperature inside the human body have been studied, particularly in the past decade. Most of these efforts seem to have been focused on the development of an applicator capable of heating deep tumors with accuracy. However, there are several problems that make it difficult to achieve deep and accurate heating. These problems include skin-depth restriction based on the skin effect and the presence of insulating materials such as lipid, protein, and bones in the human body for dielectric-type heating. In addition, eddy currents cause hot spots in unexpected regions.

As for techniques of measuring temperature, both invasive and noninvasive methods have been investigated. Invasive thermometers need lead wires to couple them either electrically or optically to an external monitor. The invasive thermometers must be sterilized prior to insertion into the patient. The patient tolerance for needle insertion is often low, limiting the number of measurement points in the tumor and, thus, limiting the thermal dose assessment. Among invasive methods, there are thermometers using thermocouples, thermistor, and fluorescent materials. Noninvasive thermometers include those that explore the use of magnetic resonance imaging (MRI) and microwave (MW) radiometry [3], [4]. These promising methods are under development.

In Japan, development of heating devices have been intensively investigated, including an RF capacitive and an microwave heating (MWH) device with a lens applicator, an RF intraluminal heating device, an RF current interstitial heating device, a ferromagnetic implant heating device, and MW interstitial heating devices. The former three devices have been approved as medical equipment for the clinical use from the Ministry of Health and Welfare of Japan. Hyperthermic treatment for cancer using electromagnetic (EM) waves is now covered by health insurance in Japan, and a large amount of clinical data has been accumulated. In this paper, we will discuss heating devices developed in Japan, and also describe the current status of clinical applications in cancer therapy.

## II. Heating Devices

Various techniques for producing localized or regional hyperthermia, including annular array using MWs, inductive RF heating, and capacitive RF heating have been developed. However, each technique has its own inherent advantage and disadvantage, and its use should be chosen based on its clinical site and tissue composition. Heating methods are divided into external, intraluminal, and interstitial heating.

### A. External Heating Devices

*1) Dielectric-Type Heating:* External heating administers heat to the tumor through various body structures. Delivery of heat energy to superficially located tumors is relatively easy.

Manuscript received October 30, 1999; revised May 20, 2000.

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Publisher Item Identifier S 0018-9480(00)09529-6.

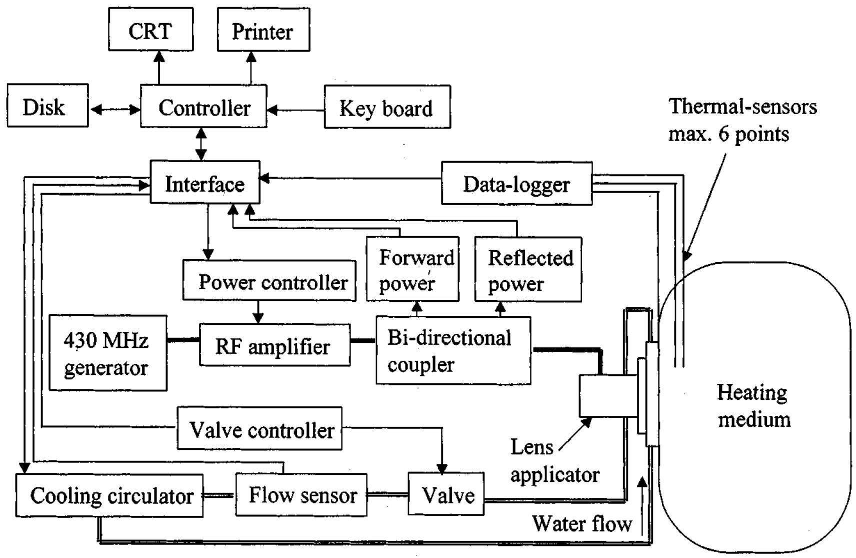



Fig. 1. 430-MHz MW heating equipment with a lens applicator.

MWH is most prevalently used for external heating of superficial tumors. One of the major problems of MWH is that the depth penetration is limited by the principle of skin-depth theory in EM wave. Only tumors located 2-3 cm from the skin surface can, therefore, be heated with a conventional surface applicator [5].

To attain deeper localized heating, metal-plate lens applicators have been developed in Japan that can converge MW energy in a lossy medium, such as human muscle, with a computer-controlled heating system [6]. Calculation of an electric-field distribution [7] and heating experiment in phantoms and miniature pigs [8] actually demonstrated a maximum heating depth of up to 6 cm with this device, which is approximately twice as deep as that obtained with a conventional waveguide applicator. This hyperthermia system consists of a 430-MHz MW generator unit with maximum output power of 500 W, a surface cooling unit, a thermometry unit, an applicator unit, and microcomputer-controlling system, as shown in Fig. 1. A four-aperture lens applicator with a total aperture size of 212 $\times$ 80 mm or a two-aperture lens applicator with a total size of 100 $\times$ 50 mm is available. The applicator is covered with a water bag, in which deionized water is circulating. The skin-surface temperature is controlled by changing the temperature of the circulating water from 10 °C–50 °C. The temperature is measured by a single-point or multipoint thin Teflon-coated copper-constant thermocouple sensor with an outer diameter of 0.8 mm. A multisensor has 3–6 separate thermocouples, with junctions located at 6-, 8-, or 10-mm intervals. During hyperthermia, MW power is switched off for 5 s every 24 s for temperature measurement.

Heat delivery to deep seated is more challenging, and major efforts have been devoted to the development of external deep-heating equipment. The ideal heating device should be capable of raising the whole tumor volume to a therapeutic temperature without overheating adjacent normal tissues.

Regional heating is the most commonly used deep-heating method. Since regional heating techniques apply energy to the adjacent deep-seated tumors in an unfocused manner, energy is also delivered to the adjacent normal tissues. Under such conditions, selective heating of tumors is only possible when heat dissipation by blood flow in normal tissue is greater than that in tumor tissue. An annular phased-array system delivering 60–80-MHz EM waves and RF capacitive heating apparatus are examples of regional heating devices. The former system has the advantage in that subcutaneous fat is not excessively heated and, thus, it is suitable for obese patients. However, this method causes systemic symptoms such as tachycardia and malaise, which result from the use of large-sized applicators. Systemic stress is reported to be more severe in patients with abdominal tumors than in those with pelvic tumors or tumors of the extremities [9], suggesting limited usefulness of this heating modality for tumors in the upper abdomen.

An 8-MHz RF capacitive heating device has been developed with a grant from the Research Development Corporation of Japan [10]. The device is schematically illustrated in Fig. 2. This equipment was approved as a medical device for thermotherapy of cancer by the Japanese Ministry of Health and Welfare in December 1984, and is now installed at over 100 hospitals in seven countries. Physical characteristics of this heating method has been described [11]. It has a self- excited oscillation circuit at 8 MHz and 1.5-kW maximum output power. The RF energy is transmitted from a generator via two coaxial cables to two disc electrodes. The RF is applied through a pair of electrodes placed on opposite sides of the body and the power is distributed locally or regionally through interaction of electric fields produced between the parallel-opposed electrodes. To facilitate heating of any site of the body, the gantry with the electrode can be rotated 180°. The adjustable positions of the electrodes and the rotation of the gantry permit heating at different angles and treatment sites. The treatment couch is motorized for vertical and horizontal movement. A portion of the top panel of the couch is opened electrically, and the lower electrode is protruded through the opening when vertical coupling is used. A pair of electrodes is connected to the pillars of the gantry. The surface of the metal plate of the electrodes is covered with a flexible water pad. Temperature-controlled water is flowing through

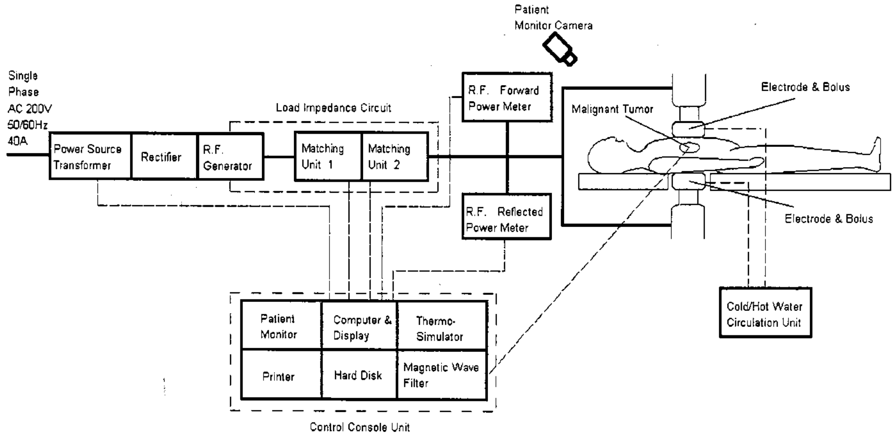
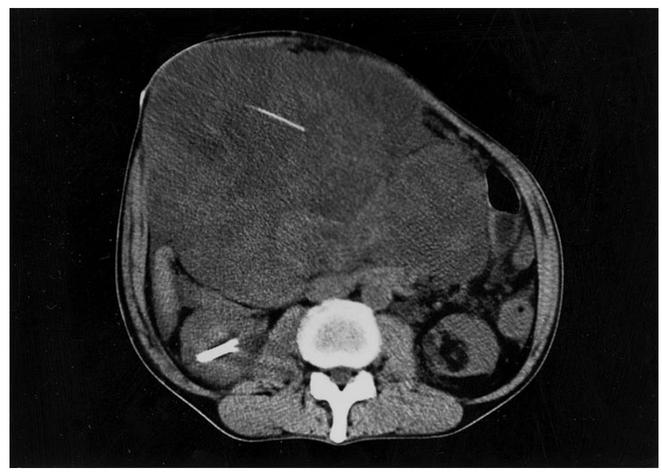



Fig. 2. 8-MHz RF capacitive heating device.

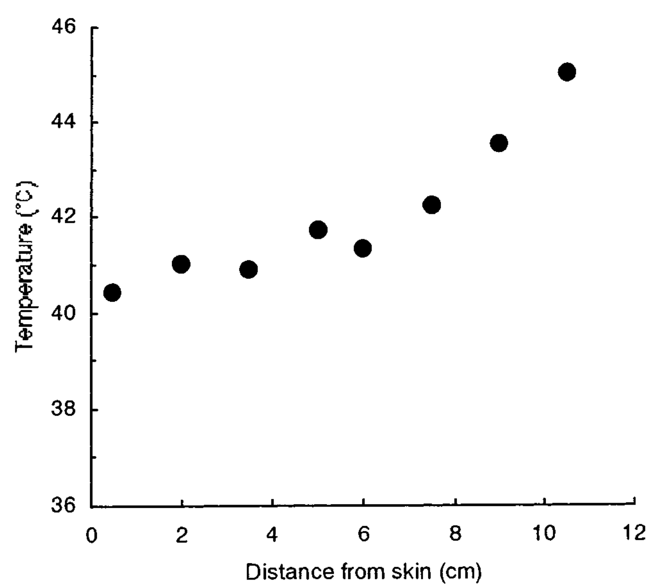
the water pad so that excessive heating of the skin and subcutaneous fat can be avoided. This pad makes it possible to smoothly attach the electrodes to the body surface. Thus, the RF energy can be supplied relatively homogeneously to an uneven site on the body. The water temperature is maintained at 30 °C–40 °C for superficial tumors and at approximately 10 °C for subsurface or deep tumors. The electrodes vary from 4–30 cm in diameter. Suitable electrodes are selected according to the size and location of the tumors. This capacitive applicator has a thermometry system with four Teflon-coated probes of copper-constant microthermocouple. The thermometry system with the microthermocouples connected to an automatic temperature-power feedback controller provides an accuracy of 0.2 °C. The high RF wave filter is inserted in the thermometry system, which is nonperturbed by RF interference and makes it possible to measure temperature even during heating. Studies made at the Minnesota University Hospital demonstrated that the measured temperature fluctuation was less than 0.45 °C when the RF current was turned on and off [12]. The temperatures measured at four points in the heated tissue are continuously displayed both graphically and digitally on the computer screen. These data are also continuously recorded on a hard disc drive, and a hard copy can be obtained on the internal printer. The power absorbed by the heated site is also continuously displayed graphically and digitally, and is recorded. An example of a thermal distribution in a human tumor treated with this device is shown in Fig. 3.

The disadvantage of RF capacitive heating is the excessive heating of subcutaneous fat, and it is shown that a patient with subcutaneous fat of more than 1.5–2 cm in thickness is difficult to heat with this heating modality [13]. The advantages are its wide applicability to various anatomical sites and relatively small systemic stress.

For tumor sites such as the neck region, where only a small amount of subcutaneous fat is present, localized RF heating will be advantageous. In dielectric-type RF applicators using a pair of circular conductive electrodes, a large-size electrode is usually needed to deeply heat a tumor uniformly. In the case of a capacitive applicator with a pair of circular electrodes, a diameter of more than 1.5 times the space between both electrodes is needed to achieve uniform heating inside the human body. For example, if the height of the heating region is 15 cm, 22.5 cm is needed as the diameter of the electrode to uniformly heat the human body in this area. If the diameter is less than this, hot spots will arise and the device cannot heat deeply.



(a)




(b)

Fig. 3. Thermal distribution of an abdominal huge tumor (MHF) treated with an RF capacitive heating device. (a) Thin catheter for the guidance of a thermometer is demonstrated in the CT image. (b) Thermal distribution was obtained by pulling out the thermometer by a 5-cm step.

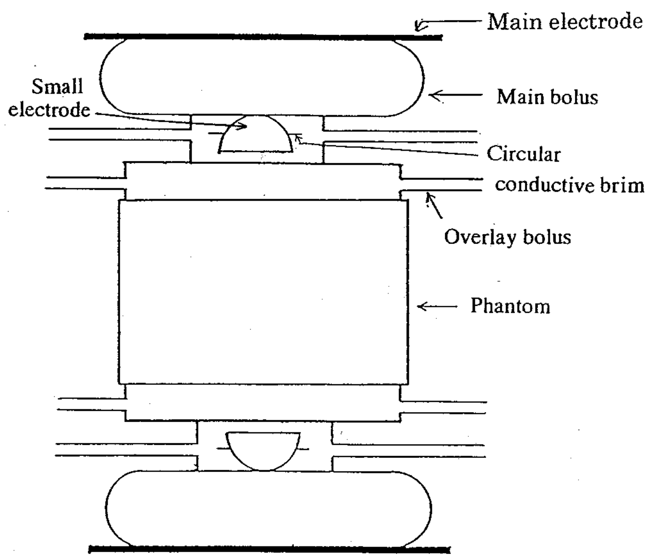



Fig. 4. Construction of new applicator with double electrodes.

To improve this, a capacitive applicator with a double electrode has been developed to achieve local heating, as shown in Fig. 4 [14]. By introducing a subelectrode consisting of a ferrodielectric material under the main electrode, an electric field can be concentrated between a pair of subelectrode or ferrodielectric materials. The size of the beam spot is proportional to the diameter of the semicircular subelectrode. If the semicircular subelectrode of 5 cm in diameter is used, a 5-cm beam of electric field over a distance of 20 cm between a pair of electrodes can be obtained.

*2) Inductive Heating:* Since magnetic fields in RF inductive heating can penetrate an insulating material such as subcutaneous fat, it can heat a tumor without heating fat tissue. A simple aperture-type applicator has been proposed using a one-turn square column-like coil made of a metal strip [15]. The operating frequency and maximum output power are 6 MHz and 7 kW, respectively. The experiment using living pigs and the clinical trials are investigated in [16] and [17].

Generally, it is difficult to achieve deep inductive heating because the eddy currents are predominantly induced near the surface of the human body. To resolve this problem, a deformed ferrite core applicator system with auxiliary electrode has been developed [18]. The operating frequency and the output power are 4 MHz and 850 W, respectively.

Deep local inductive heating can be achieved using an implant material, which generates heat by its interaction with the magnetic field. However, since eddy currents are predominantly induced near the surface of the human body, the result is that both the implanted region and superficial normal tissue are being heated. To reduce the heating of normal superficial tissue, an eddy-current absorber has been proposed [19]. This eddy-current absorber consists of silicon rubber containing a fine carbon powder. By optimizing material constant of the eddy-current absorber, the eddy currents that arise at unexpected portion of the human body can be absorbed.

Knowing that a ferrite core applicator is able to efficiently heat the inside of a protuberance on the human body, a simple applicator using a pair of ferrite cores has been developed for breast hyperthermia [19]. This applicator can regionally heat the breast, regardless of the size of the breast, without overheating fat tissue.

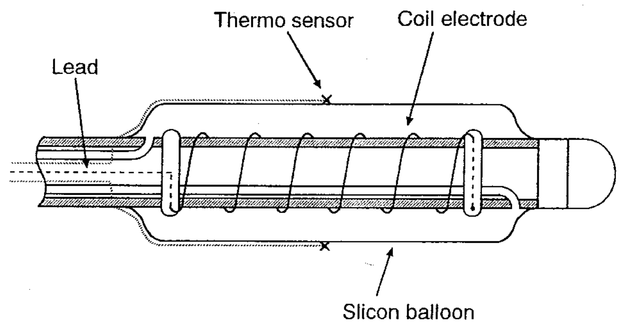



Fig. 5. Intralumonal RF electrode.

### *B. Intraluminal Heating Devices*

The second method for deep heating is an intraluminal heating using hot fluid, MW, or RF. Sugimachi *et al.* [20] have developed an RF intraluminal hyperthermia system. Very localized heating is possible with this device by inserting an endotract electrode into lumens of the human body, such as the esophagus, rectum, and uterine cervix. A wide counter electrode is placed on the skin surface of the body so that the RF flux concentrates around the endotract electrode. Various types of electrodes are available depending on the size of the lumen and the site of the lesion. An electrode is connected to the RF system, which is operated at the frequency of 13.56 MHz with a maximum power of 250 W. The main structure of the electrode consists of the following three parts, as shown in Fig. 5:

1) transmitter for RF irradiation;
2) balloon and cooling system, which eliminates the gap between malignant tissues and the transmitter (60 ml/min of water at the room temperature is circulated to prevent overheating of the transmitter);
3) thermosensor: copper/constant microthermocouples were fixed to the outside of the balloon.

Recently, a new intraluminal electrode has been developed that enables us to undertake simultaneous thermoradiotherapy. A high-dose rate irradiation source (192 Ir) can be introduced inside this electrode.

### *C. Interstitial Heating Devices*

The third method is interstitial heating, which is divided into RF current heating, MWH, and ferromagnetic implant heating. The advantages of interstitial heating are: 1) selective heating of localized tumors and 2) feasibility of combined use of brachytherapy. On the other hand, the disadvantages are: 1) invasiveness; 2) difficulty in repeated treatment; and 3) limitation of applicable sites.

As an interstitial heating devices, a fine coaxial line with small slots of about 1 mm in a outer conductor has been developed [21]–[23]. The operating frequency is 430 MHz. Ferromagnetic implant heating is being investigated in Japan. They have developed an implant heating system (IHS), which consists

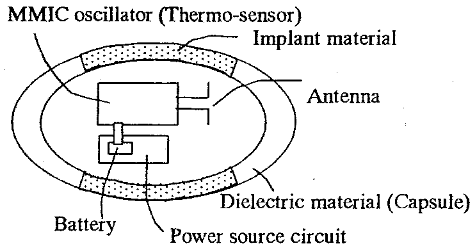



Fig. 6. Wireless thermometer with implant function using a three-dimensional MMIC.

of a ferromagnetic implant, induction coil, and generator to produce a high-frequency magnetic field. The implant is made of Fe–Pt alloy (Fe: 73%, Pt: 27%), and has a Curie temperature of 68 °C. This system is being clinically investigated for the treatment of brain tumors [24] and tongue cancers [25].

One of the important problems to overcome in hyperthermia is to achieve an accurate deep local heating together with exact measurements of temperature. A wireless-thermometer using a monolithic microwave integrated circuit (MMIC) with an implant function has been proposed from these viewpoints [26], as shown in Fig. 6. As a temperature sensor, a silicone MMIC with a voltage-controlled oscillator (Si MMIC VCO) has been introduced. Its size is very small, i.e., $2 \times 2$ mm. This has a special feature in that the thermometer is a very simple construction because the Si MMIC VCO acts as a temperature sensor, thus, the thermometer can be constructed without a transmitter or amplifier. As a wireless thermometer, it can measure the temperature accurately without noise interference induced by a lead wire carrying irradiated EM waves from an applicator.

## III. Clinical Applications: Superficial and Subsurface Tumors

A large number of clinical experiences with combined hyperthermia and radiation therapy have been reported for superficial and subsurface tumors. Treatment of superficial tumors offer significant advantage as compared to the treatment of deep-seated tumors. Well-developed heating devices are available for their treatment, and these tumors are easy to both heat and to place thermometers into. The response of superficial tumors to the combined treatment is relatively easy to assess and, therefore, they provide a good model to investigate the combined effectiveness of hyperthermia and radiation. Additionally, several superficial tumors, including malignant melanoma, soft-tissue tumors, locally advanced tumors, and recurrent tumors following radiation therapy are still resistant to conventional treatments. The combined hyperthermia and radiation therapy offers potential clinical advantages for the treatment of these tumors.

Usefulness of thermoradiotherapy was initially demonstrated by several trials, including our trial in patients with two or more comparable tumors (matched tumors) [27]. Approximately a twofold increase in local response rates was shown in thermoradiotherapy than in radiotherapy alone. In addition to these studies, prospective randomized trials have been recently performed. A trial carried out by the Radiation Therapy Oncology Group (RTOG) in the U.S. failed to show a difference in the response rate between radiation alone and radiation plus heat when the tumors treated were analyzed all together [28]. When the tumor response was assessed according to the tumor size, a significantly higher response rate was achieved with the combined hyperthermia and radiotherapy for tumors with maximum diameter less than 3 cm, but not for tumors more than 3 cm in diameter. On the other hand, however, it was pointed out that to evaluate tumor response after the thermoradiotherapy, appearance of low-density area (LDA) on computed tomography (CT) images are more important than the actual shrinkage of tumor volume [29]. The combined treatment also showed a substantially higher response rate in breast tumors, but not in head and neck tumors or other tumors in comparison with radiotherapy alone. Since smaller tumors and breast lesions are easier to heat, it is suggested that heating limitation may be the reason for the lack of enhanced effects of combined treatment for large tumors and nonbreast lesions.

The other randomized trials including an international trial for breast cancer [30], a European Society for Hyperthermic Oncology (ESHO) trial for malignant melanoma [31], a Japanese Society for Therapeutic Radiology and Oncology (JASTRO) trial for superficial tumors [32] have clearly demonstrated the improvement of local control rate with the use of hyperthermia. Additionally, no enhancement of normal tissue damages by radiation was found. Thus, clinical benefits of hyperthermia combined with radiotherapy appear established for superficial tumors.

## IV. Clinical Applications to Deep-Seated Tumors

Site-specific trials have been undertaken. A summary of those trials is shown in Table I.

### A. Trials for Esophageal Cancers

Using an RF intracavitary heating device, Sugimachi *et al.*have applied hyperthermia in combination with radiotherapy and chemotherapy to patients with esophageal carcinoma. The long-term results were compared between two groups of patients treated with hyperthermo-chemo radiotherapy (HCRT) and those with chemo radiotherapy (CRT). The five-year survival rates of patients with respectable carcinoma, given preoperative HCRT or CRT, were 43.2% and 14.7%, respectively ($p < 0.05$). The two-year survival rates of those with unresectable carcinoma and receiving HCRT or CRT were 15.5% and 1.2%, respectively [33]. A prospective randomized trial was carried out to examine the effects of hyperthermia given preoperatively. Sixty-six patients with esophageal cancer underwent subtotal esophagectomy following either preoperative HCRT or CRT therapy. The incidence of lack of viable cancer cells in the resected specimens was 25% in the HCRT group and 5.9% in the CRT group. The cumulative three-year survival rate was 50.4% in the HCRT group and 24.2% in the CRT group [34].

### B. Trials for Lung Cancers

It has been shown that RF capacitive heating devices can effectively raise temperatures of invasive lung tumors that were in

TABLE I
SUMMARY OF CLINICAL REPORTS FOR DEEP-SEATED TUMORS

A. Esophageal Cancer

| Authors | Tumor type | No. of patients | Heating methods | Combined treatment | Survival rate | |
|---|---|---|---|---|---|---|
| Kuwano M et al.1993 | resectable tumor | 183 | intraluminal RF capacitive | chemoradiotherapy | 5Y | 43.2% |
| | unresectable tumor | 114 | intraluminal RF capacitive | chemoradiotherapy | 2Y | 15.5% |
| Kitamura K et al.1995 | resectable tumor | 66 | intraluminal RF capacitive | chemoradiotherapy | 3Y | 24.2% |

B. Lung Cancer

| Authors | No. of patients | Heating methods | Combined treatment | Response rate (CR + PR) | Complication |
|---|---|---|---|---|---|
| Hiraoka M et al.1992 | 20 | RF capacitive | radiotherapy | 75% (17%+58%) | pain,dyspnea |
| Karasawa K et al.1994 | 19 | RF capacitive | radiotherapy | 95% (26%+69%) | |

C. Liver Cancer

| Authors | Tumor type | No. of patients | Heating methods | Combined treatment | Response rate (CR + PR) | Survival rate | | Complication |
|---|---|---|---|---|---|---|---|---|
| Nagata Y et al.1997 | HCC | 73 | RF capacitive | chemoradiotherapy | 31% (10%+21%) | 1Y<br>5Y | 30%<br>17.5% | local pain |
| | non-HCC | 45 | RF capacitive | chemoradiotherapy | 45% (7%+38%) | 1Y | 32.5% | |
| Kondo M et al.1993 | metastatic tuomor from colorectal cancer | 14 | RF capacitive or Total body hyperthermia | chemotherapy | 57% | Median 23months | | pain,fever |
| Tanaka K et al.1992 | HCC | 18 | RF capacitive | Intra-arterial chemotherapy (DSM) | 56% | | | fever,epigastralgia mostly related to embolization |
| Yumoto Y et al.1991 | HCC | 20 | RF capacitive | Intra-arterial chemotherapy (TAE) | 40% | | | fever,pain, myelosupression |

HCC : Hepatocellular carcinoma DSM : degradable starch microspheres TAE : transarterial embolization

D. Gastric Cancer

| Authors | Tumor type | No. of patients | Heating methods | Combined treatment | Response rate (CR + PR) | Survival rate | |
|---|---|---|---|---|---|---|---|
| Hamazoe R et al.1991 | peritoneal dissemination | 11 | continuous hyperthermic peritoneal perfusion | chemotherapy | better than chemotherapy alone | | |
| Kakehi M et al. 1990 | gastric cancer | 33 | RF capacitive | chemotherapy | 39% (9%+30%) | | |
| Nagata Y et al.1995 | inoperable gastric cancer | 21 | RF capacitive | chemotherapy | 89% | 1Y | 39.1% |

contact with the chest walls. We reported clinical results of 20 patients with lung cancer treated by thermoradiotherapy [35]. The mean of $T_{\max}$, $T_{\text{ave}}$, and $T_{\min}$ was 42.9 °C, 41.6 °C, and 39.7 °C, respectively. Of 12 tumors treated by a curative intent, two (17%) achieved complete response (CR), seven (58%) partial response (PR), and three (25%) no change (NC). The side effects associated with hyperthermia were pain in 12 patients (60%) and dyspnea in three (15%), all of which resolved after termination of treatment.

Improvement of local response rate [36] and survival rate [37] has been demonstrated with the combined treatment of regional hyperthermia and radiation therapy in nonrandomized trials.

TABLE I *(Continued.)*
SUMMARY OF CLINICAL REPORTS FOR DEEP-SEATED TUMORS

E. Colorectal Cancer

| Authors | Tumor type | No. of patients | Heating methods | Combined treatment | Response rate (CR + PR) | Survival rate | Complication |
|---|---|---|---|---|---|---|---|
| Nishimura Y et al.1995 | recurrent colorectal cancer | 71 | RF capacitive | radioherapy | 54% | | ileus,fistula |
| Ohno S et al. 1997 | resectable tumor | 88 | intracavitary hyperthermia | chemoradiotherapy | | 5Y 91.3% | |

F. Urinary Bladder Cancer

| Authors | Tumor type | No. of patients | Heating methods | Combined treatment | Response rate (CR + PR) |
|---|---|---|---|---|---|
| Masunaga S et al.1994 | resectable tumor | 49 | RF capacitive | radiotherapy | 83% (Tave.>41.5℃) |

G. Soft Tissue Tumors

| Authors | Tumor type | No. of patients | Heating methods | Combined treatment | Response rate (CR + PR) | Survival rate 5Year |
|---|---|---|---|---|---|---|
| Hiraoka M et al.1995 | unresectable tumor | 31 | RF capacitive | Chemoradiotherapy | 74% (42%+32%) | 5Y 48% |

### C. Trials for Liver Tumors

Heating capability of the 8-MHz RF capacitive device was evaluated for 77 liver tumors. The maximum tumor temperature, average tumor temperature, and minimum tumor temperature in the hepato cellular carcinoma (HCC) were (mean $\pm$ standard error) 41.2±0.2 °C, 40.3±1.3 °C, and 40.1±0.2 °C, respectively. The same thermometry results for non-HCC were 42.3±0.2 °C, 41.2±0.2 °C, and 40.9±0.2 °C, respectively. The maximum and minimum temperatures (41.8± 0.2 °C and 40.3±0.4 °C) in the patients with a CR or PR were higher than those in the patients with no response (NR) or progressive disease (PD) (41.2±0.5 °C and 39.8±0.4 °C), but the difference was not significant.

Of the 73 cases with HCC who were evaluated by CT, CR was achieved in 7 (10%), PR in 15 (21%), NR in 37 (51%), and PD in 14 (19%).

Of the 45 cases involving liver metastases evaluated by CT, CR was achieved in 3 (7%), PR in 17 (38%), NR in 12 (27%), and PD in 13 (29%). The one-year cumulative survival rate for HCC patients was 30.0%, and the five-year survival rate was 17.5%. The one-year survival of non-HCC patients was 32.5%, and the longest survival was 30 months. The sequelae of hyperthermia included focal fat necrosis in 20 patients (12%), gastric ulceration in four (2%), and liver necrosis in one (1%). The sequelae of thermometry were severe peritoneal pain in seven patients, intraperitoneal hematoma in one, and pneumothorax in one [38].

A number of strategies have been proposed that might lead to an selective heating of tumors. One of these is a manipulation of blood flow by degradable starch microspheres (DSMs). A DSM is a cross-linked starch microsphere with a mean diameter of 45 $\mu$m. It is dissolved by a $\alpha$-amylase in the serum with a biological half-life of 15–30 min. Blood flow in tumors is shown to decrease transiently, leading to an increase in heating when DSM is administered in a feeding artery of tumors during hyperthermia. The accelerated increase in the liver temperature in accordance with the administration of DSM in the common hepatic artery during regional hyperthermia has been demonstrated in an experiment using pigs [39]. A clinical trial showed that transarterial embolization (TAE) with DSM helped 0.9 °C increase in the maximum tumor temperature [40].

The usefulness of combined treatment of intra-arterial chemotherapy and hyperthermia have been suggested in several clinical reports [41].

Complications were mostly related to the chemoembolization with DSM, which included fever, epigastric pain, and so on [38].

The clinical benefit of combined treatment of hyperthermia and TAE has been demonstrated in a randomized trial. Twenty patients were randomly assigned to either hyperthermia plus TAE or TAE alone. Regional hyperthermia was administered at tumor temperatures of more than 42.5 °C for 40 min twice a week, to a total of 10–38 sessions. The response rate was 40% in the ten patients treated by hyperthermia plus TAE and 20% in the ten patients treated by TAE alone. The patients treated by hyperthermia plus TAE had a tendency to have better survival rates than those of the TAE group. The main side effects of TAE plus hyperthermia were low-grade fever, localized pain, myelosupression, and liver dysfunction, but these were transient and eventually resolved [42].

### D. Trials for Gastric Cancers

The heating capability of Thermotron RF-8 for peritoneally disseminated tumors from gastric or colorectal tumors was investigated. Tumor temperatures were measured by thin Teflon-coated microthermocouples, which had been implanted under laparotomy or inserted transcutaneouly under ultrasonography into the center of the tumors. Of six tumors heated, tumor temperature could be raised over 43 °C in one tumor, 42 °C–43 °C in one tumor, and less than 42 °C in the remaining four tumors [43].

Hyperthermia in combination with chemotherapy was applied to 33 patients with gastric cancer. Hyperthermia was regionally given twice a week to a total of 6–40 sessions using an 8-MHz RF capacitive heating device. Chemotherapy consisted of mitomycin C (MMC) and 5-FU derivatives. Of the 33 patients treated, three (9%) showed CR and ten (30%) PR [41].

Recurrent and/or inoperable gastric cancer has been treated by thermoradiotherapy at Kyoto University Hospital, Kyoto, Japan, since 1983. The local response rate (complete regression plus partial regression/all tumors) was 88.9%, which seemed to be higher than that of other reports using thermochemotherapy or radiotherapy alone. The one-year cumulative survival rate was 39.1% [44].

### *E. Trials for Colorectal Cancers*

The efficacy of RF capacitive heating is high for pelvic tumors, especially for large recurrent colorectal cancers.

We have treated 71 patients with unresectable or locally recurrent colorectal cancer by radiotherapy with or without locoregional hyperthermia [45]. Thirty-five patients were treated by radiotherapy plus hyperthermia (group I), while 36 patients were treated by radiotherapy alone (group II), mainly because of difficulties with the insertion of temperature probes or the thickness of the patients subcutaneous fat. The total radiation dose did not differ between groups I and II, but the mean tumor volume was significantly larger in group I than in group II. The incidence of freedom from local tumor regression at six months after the treatment was 59% (17/29) and 37% (11/30) for group I and group II, respectively. The objective response rate (CR + PR) was 54% (19/35) in group I, whereas it was 36% (10/28) in group II. A higher response rate of 67% was obtained in the 15 tumors with a $T_{\mathrm{ave}}$ of more than 42 °C compared with 47% for 17 tumors with a $T_{\mathrm{ave}}$ of less than or equal to 42 °C, although this difference was not significant. The incidences of obstructive ileus and intestinal fistula were relatively higher in group I (20%, 8.5%) than in group II (3%, 0%).

The usefulness of RF intracavitary hyperthermia combined with chemotherapy and radiotherapy as a preoperative treatment for rectal cancer has been investigated [46]. Postoperative prognoses were compared among 36 patients with carcinoma of the rectum, who were given preoperative HCR therapy followed by surgery, and 52 patients undergoing surgery alone without any preoperative therapy. There were significant differences in the prognosis between patients given preoperative HCR therapy plus surgery and those having surgery alone, and five-year survival rates were 91.3% and 64%, respectively. Particularly for patients with tumors invading beyond the muscularis propria and/or with positive lymph node metastasis, a significantly longer survival was obtained with HCR plus surgery than in surgery alone (86.5% versus 50.9% and 92.9% versus 51.7%, respectively). However, no significant differences were observed in the postoperative prognosis for cases with no lymph-node metastasis and/or with tumors limited to the muscularis propria between these two groups.

### *F. Trials for Urinary Bladder Cancers*

Most trials for urinary bladder cancers were undertaken with the use of RF capacitive heating devices.

Preoperative radiotherapy or thermoradiotherapy was administered to 49 patients with bladder cancer. Twenty-eight patients were treated by radiation therapy combined with hyperthermia (group I). Radiation therapy was delivered with 4-Gy per fraction, 3 fractions per week to a total dose of 24 Gy ($\mathrm{TDF} = 53$). The other 21 patients were treated by the same radiation therapy regimen without hyperthermia (group II). Regional hyperthermia was administered for 35–60 min immediately after irradiation (two sessions per week to a total of four sessions) using an 8-MHz RF capacitive heating device. Group I was divided into group I (High), in which the average intravesical temperature ($T_{\mathrm{ave}}$) was above 41.5 °C (12 patients), and group I (Low) with a $T_{\mathrm{ave}}$ below 41.5 °C (16 patients). The incidence of down-staging for group I (High), group I (Low) and group II was 83%, 38%, and 48%, and that of tumor degeneration was 83%, 44%, and 40%, respectively. The differences in response rate between group I (High) and the other groups were significant ($p < 0.05$). Survival rate tended to be higher in the group I than in the group II. This trend is more apparent for those cases with T3–4 or Grade-3 bladder cancer for which preoperative treatment is considered to be more indicated [47].

### *G. Trials for Soft Tissue Tumors*

We have treated 31 unresectable and/or recurrent soft tissue tumors in 27 patients by hyperthermia in combination with radiation therapy. Tumor volume ranged from 3 to 3927 $\mathrm{cm}^3$, with a mean of 428 $\mathrm{cm}^3$. Locoregional hyperthermia was delivered once or twice a week for 40–60 min to a total of 2–14 sessions. Radiation therapy was given at doses of 20.8–70 Gy. The mean of $T_{\max}$, $T_{\mathrm{ave}}$, $T_{\min}$ was, respectively, 44.0 °C, 42.3 °C, and 40.1 °C. Of the 31 tumors treated, 13 (42%) showed CR, 10 (32%) PR, and 8 (26%) NC. Of 20 tumors in which the early response to thermoradiotherapy was assessed by X-CT, massive intratumoral low-density areas reflecting coagulation necrosis by hyperthermia was shown in six (30%) tumors. All of these tumors demonstrated a marked response on follow-up or histopathological examinations. Thermal parameters were more influential than the total irradiation dose in terms of both tumor regression and the appearance of intratumoral low-density areas. The five-year survival of 18 patients who had no distant metastases at the start of treatment was 48% [48].

## V. CONCLUSION

Technical and clinical aspects for hyperthermia techniques used in Japan have been reviewed in this paper. Several methods of improving the heating characteristics from the various heating device have been proposed. Regional heating can be efficiently achieved by using RF capacitive techniques. That is because regional heating techniques apply energy to the adjacent deep-seated tumors in an unfocused manner and energy is also delivered to the adjacent normal tissue. This condition makes it possible to realize selective heating of tumors when heat dissipation by blood flows more predominant than in normal tissue. A double-electrode capacitive applicator has been proposed to attain deep heating locally.

To avoid fat tissue heating, inductive heating is effective. However, the eddy current has a tendency of distributing near the surface of the human body due to its inherent nature. As a result, hot spots arise near the surface of the human body. To prevent this phenomena, the eddy current was controlled by introducing an auxiliary electrode and eddy-current absorber.

When using hyperthermia, it is important to establish accurate local and deep-heating techniques and to be able measure the temperature distribution throughout the heated volume. To attain this goal, a wireless thermometer with an implant function was proposed, although this is an invasive method. A future goal is to use MRI and spectroscopic techniques for noninvasive mapping of the temperature distribution.

Many clinical trials have been introduced with detailed investigation of the response rate.

Nonrandomized trials undertaken in Japan for locally advanced breast cancers, esophageal cancers, lung cancers, liver tumors, gastric cancers, unresectable, or recurrent colorectal cancers and invasive urinary bladder cancers demonstrated higher response rate in thermoradiotherapy than in radiotherapy alone. Randomized trials have been carried out for esophageal cancers and gastric cancers, and both of them showed improved local response with the combined use of hyperthermia. Additionally, the complications associated with treatment were not generally serious, except for chronic bowel damages suggested in a trial for colorectal cancers. These clinical results indicate the benefit of combined treatment of hyperthermia and radiotherapy for various malignancies.

The use of heat in cancer therapy is the subject of an ever-broadening multidisciplinary research effort involving the fields of biology, physics, engineering, and medicine. There are many questions still to be answered regarding biological issues such as thermotolerance and thermal dose. Major efforts should be devoted to the development of a device that is capable of raising the whole tumor volume to therapeutic temperatures without overheating the adjacent normal tissues. With the advancement of these technologies, hyperthermia will be more widely and safely used in the treatment of cancers.

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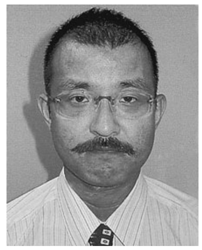

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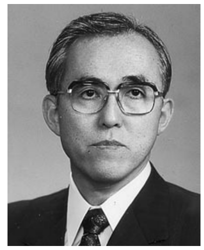

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