Br. J. Cancer (1982) **45**, Suppl. V, 71

RADIOFREQUENCY DIATHERMY FOR UNIFORM HEATING OF MOUSE TUMOURS

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Summary.—A system has been developed for uniformly heating mouse tumours by using a combination of 27·12 MHz radiofrequency electric fields (RF) and immersion in heated liquid. Continuous tumour thermometry with implanted thermocouples is necessary in order to modulate the RF power to maintain a constant temperature over 1 h.

Tumours implanted intramuscularly in the hind limbs of mice were heated between a pair of 1·9cm diameter parallel copper plates. The optimum temperature profile was achieved if the RF heating was combined with immersion of the limb in circulating saline, preheated to the desired temperature. This method of electrical coupling between the plates and tissues has been shown to be significantly better than using ECG jelly or unheated liquid, and it is better than simple immersion in heated liquid without RF.

A temperature monitoring system has been developed, using fine thermocouples implanted into the tumour, to regulate the applied RF power. Each complete thermocouple probe is less than 0·5mm in diameter and consists of 6 separate monitoring junctions spaced at 1·5mm intervals along its length. Using this monitoring system the temperature within tumours has been maintained constant (±0·1°C) for a period of 1 h.

THE USE of hyperthermia as an adjunct to radiotherapy and chemotherapy of cancer is of great clinical interest. The field is hindered by the difficulty of achieving uniform temperatures, even in small experimental tumours in mice or rats. Immersion in hot water is often used in experimental studies. However, temperature variations of up to 2°C have been reported within subcutaneous and intramuscular tumours after waterbath immersion (Bleehen *et al.*, 1977; Robinson *et al.*, 1978; Hill *et al.*, 1980; Joiner, 1980). Since "hot spots" will damage normal tissues excessively and "cold spots" will protect clusters of tumour cells (Bleehen *et al.*, 1977; Hume *et al.*, 1979; Hill *et al.*, 1980) it is necessary to develop systems for producing uniform temperature distributions at the desired temperature for periods of about 1 h. We have achieved this object by using a combination of RF heating and liquid immersion, with continuous temperature monitoring.

MATERIALS AND METHODS

Tumour system.—The RF heating was evaluated *in vivo* using the transplantable tumour, Sarcoma F, growing in the gastrocnemius muscle of the limbs of specific pathogen free CBA mice (CBA/HtGyfBSVS). Ten min before heating, the mice were anaesthetized by intraperitoneal injection of sodium pentobarbitone at a dose of 60 mg kg^{-1}.

RF heating system.—Fig. 1 shows the heating system we have developed. Mice were heated individually. Each mouse was laid in a supporting cradle positioned on the RF heating jig so that the tumour-bearing leg lay between two 1·9 cm diameter circular copper plates. The jig is arranged so that the space between the electrodes and the tumour can be filled with electrolyte solution, which can be circulated continuously via an external, separately thermostated heater if required. RF power at 27·12 MHz was produced by a conventional oscillator and power amplifier, with an output impedance of 50 Ω. We found the electrical impedance of tumours in these jigs to be approximately 100 Ω each, therefore

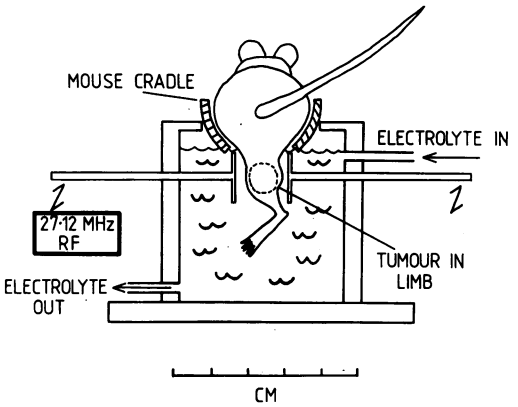

FIG. 1.—The RF heating system.

a 1:2 impedance matching transformer was used to couple the amplifier to the heating electrodes.

Temperature monitoring.—In order to assess temperature distributions directly, we constructed fine (0·5 mm overall diameter) probes consisting of 6 thermocouple junctions located at intervals of 1·5 mm along the length of the probe. These probes were inserted into the tumours via a 25 gauge hypodermic needle which was then withdrawn, leaving the probe embedded. The 6-way probe was connected to a direct reading thermocouple amplifier (Bailey Instruments, Saddle Brook, N.J., U.S.A.), and the thermocouple outputs could be switched to read temperatures at different depths in each tumour. Readings were made in short periods (~3 sec) during which the RF was turned off.

RESULTS AND DISCUSSION

Tempcrature distribution in tumours

Temperature distributions were measured through the centre of tumour-bearing legs for several different heating arrangements. These are illustrated in Fig. 2 for heat applied by RF alone using two different coupling agents, by liquid immersion alone and for a combination of immersion and RF heating.

Initially, ECG jelly ("Camjel", Cambridge Medical Instruments Ltd, Royston, Herts) was used to couple the RF electrodes to the tumour-bearing leg. A 2–3mm thick layer of jelly was packed into the gap between the electrodes and the leg and those parts of the leg not touching the jelly were left in contact with the surrounding air at room temperature. The steady-state temperature distribution obtained with an applied RF power of approximately 1 W cm^{-2} is shown in Fig. 2a; these values were observed after approximately 5 min and were markedly non-uniform. The highest temperature occurred in the tumour centre with peripheral areas being 5–20°C lower in the different tumours. This non-uniformity is much greater than that found with conventional heating by immersion in hot water and goes in the opposite direction. Fig. 2b shows temperatures in the central region of tumours after 20 min heating by immersion in dilute saline (without RF) at 43·0°C (controlled to ±0·1°C) to be 1·5–2·0°C below the water temperature. In an attempt to overcome the large temperature gradients with RF alone, tumour-bearing legs were heated whilst immersed in a bolus of weak saline (0·043% w/v), which we found to be approximately electrically equivalent to the tumours at 27 MHz. The temperatures shown in Fig. 2c were reached within 30 min, using an applied power of approximately 1 W cm^{-2}. The temperature across the tumour was now more uniform but the saline temperature was lower than the tumour temperature, in spite of being in the same RF field.

Although the RF power needed to produce a given temperature in the saline is determined by its electrical conductivity and the geometry of the jig, the power needed to maintain a given tumour temperature varies from tumour to tumour, possibly because of differences in blood flow. In animals that were killed *in situ* while their tumours were being heated by RF, the temperature at the tumour centre rose by 2°C as the blood flow ceased. Differences in blood flow between tumours would make it difficult to obtain equal temperatures in all the tumours and a static saline bolus by RF heating alone. Furthermore the method

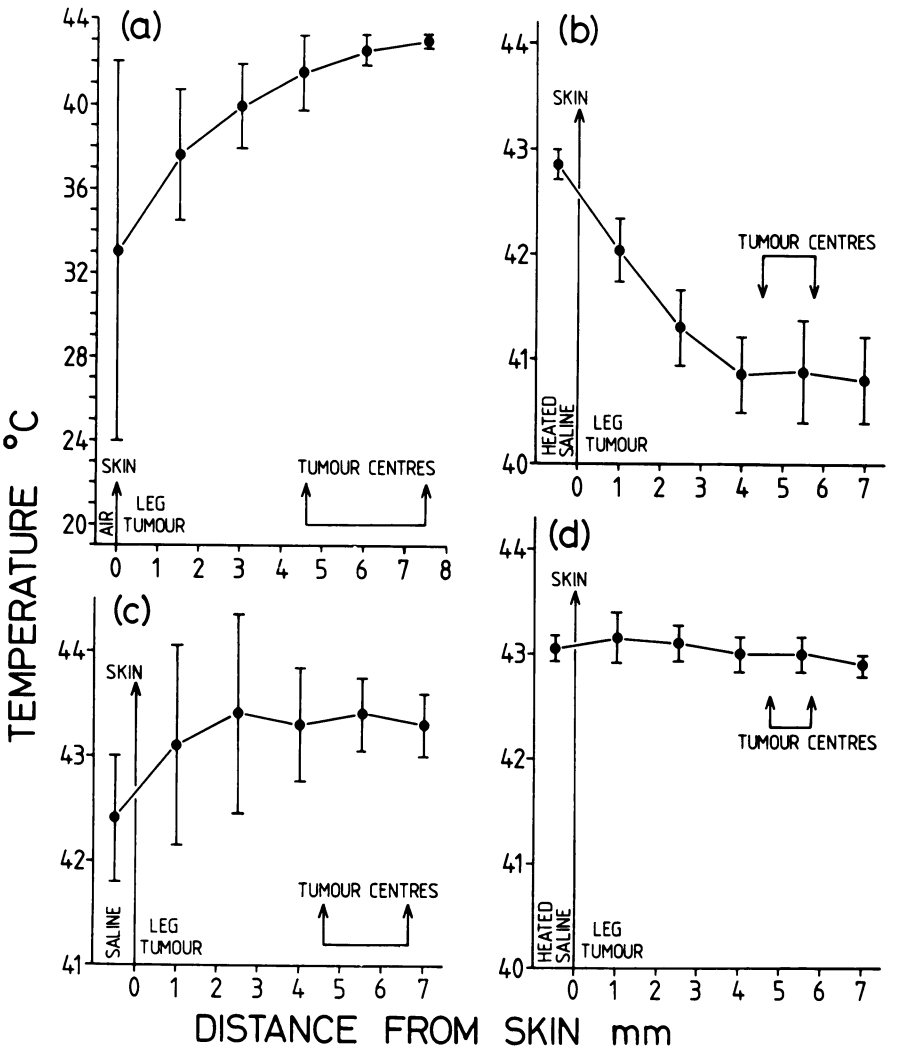

FIG. 2.—Temperatures within heated tumours. Mean ± 95% confidence limits. Methods of heating/electrical coupling are (a) RF alone/ECG jelly (5 tumours); (b) liquid immersion (43·0°C) alone (7 tumours); (c) RF alone/static saline bolus (5 tumours); (d) RF/saline + liquid immersion (43·0°C) (7 tumours). Arrows give the positions of the skin and the range of centres for the different tumours.

has the disadvantage that long times (30 min) are required to raise the temperature in the tumour, due to the extra volume of saline bolus that must be heated.

Since the temperature gradients are in opposite directions for immersion heating and for RF heating, we adopted the method of heating the saline coupling medium by circulating it through an external heater. In this case, the temperature of the saline surrounding the tumour (controlled by the external heater) and the temperature within the tumour (controlled by the RF power) could be varied independently of one another. Fig. 2d shows the temperature distributions achieved with this method. The saline was preheated to 43·0°C and the RF intensity increased until the temperature

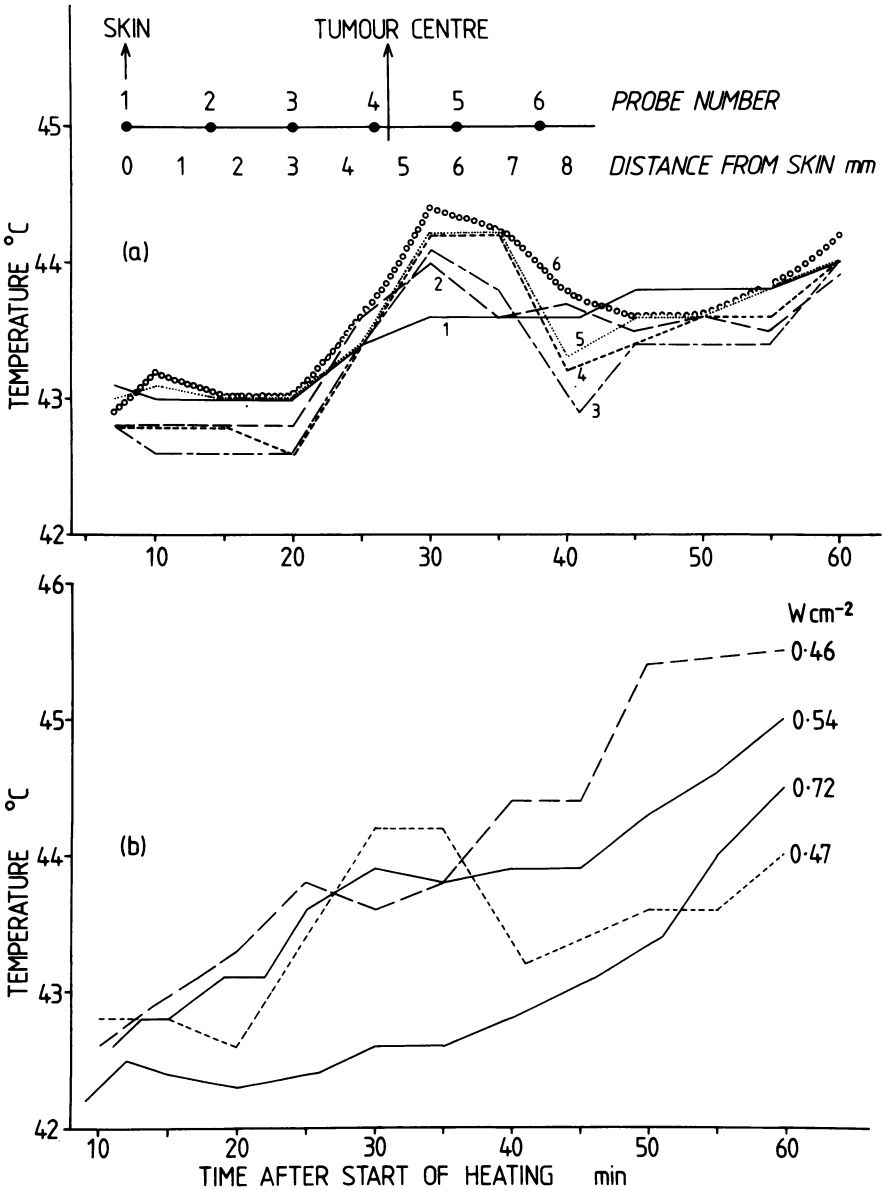

FIG. 3.—Variation of temperature with time in RF-heated tumours. (a) 6 measurements in one tumour (RF intensity = 0·47 W cm^{-2}); (b) measurements at the centre of 4 tumours heated by various RF intensities.

in the tumour centre reached 43°C. This was achieved with an intensity of 0·5–0·8 W cm^{-2} within 3 min. The temperature uniformity in the tumour-bearing leg was better than $\pm$ 0·2°C. We conclude that a combination of simultaneous heating by 27 MHz RF and immersion in warmed and circulating liquid can provide good temperature uniformity in experimental tumours. A similar approach has been described for microwaves by Robinson *et al.* (1978) and Hand *et al.* (1979) and the

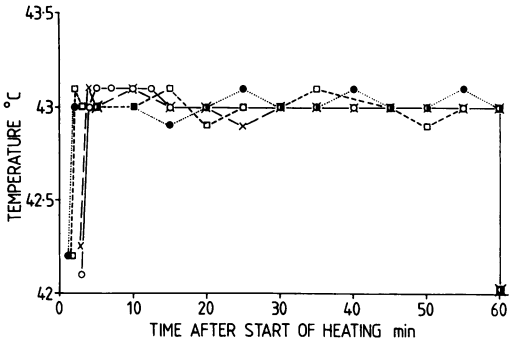

FIG. 4.—Variation of temperature with time in 4 different SaF tumours heated by RF and thermostatically regulated to 43 °C.

method might also be useful to improve temperature uniformity in small animal tumours heated by ultrasound, where temperature distributions are similar to those in Fig. 2a (Joiner, 1980).

Fluctuations in tumour temperature

For hyperthermia treatments it is necessary to maintain a desired temperature within narrow limits for a prolonged period, as well as to achieve a uniform distribution. In order to assess the variation in tumour temperature with time during RF heating, several tumours were immersed in weak saline maintained at 43·0 °C and then heated with RF for 1 h in our jigs. An initial "boost" of power (1·2–1·3 W cm^{-2}) was given during the first 2 min to bring tumour temperatures quickly into the range 42°–43 °C. RF power was subsequently maintained at the constant levels shown in Fig. 3b for 4 separate tumours. Fig. 3a shows the readings from the 6 separate thermocouples within one tumour. Considerable fluctuations in tumour temperature were observed, with a trend towards higher temperatures at later times, but with some unpredictable drops, even when the RF intensity was held steady. Furthermore, we found no correlation between temperature and RF intensity in the examples shown; higher RF intensities did not necessarily result in higher tumour temperatures. These results illustrate the need for thermostatic regulation to modify the RF power *during* treatment if a given tumour temperature is to be maintained.

Thermostatic control system

We are developing an electronic control system to provide continuous temperature monitoring, which can be used for thermostatic regulation during RF heating. This device measures the tumour temperature during short periods (20 ms) when the RF is turned off. Sampled tumour temperature is compared to the desired tumour temperature and if the temperature is too low the RF power is applied for a further 200 ms. If the desired temperature has been reached, or exceeded, the RF power stays off until the next temperature measurement is made. This procedure is repeated at 200 ms intervals. Provided the RF power is adequate to achieve the desired tumour temperature, a steady temperature can be maintained for a prolonged period. Similar use of tissue temperature measurements to control heat application by microwaves has also been described by Hand (1979).

Fig. 4 illustrates the results of some measurements of central tumour temperature using our system to heat tumours to 43 °C. Tumour bearing legs were immersed in the dilute saline coupling medium which was separately thermostated to 43·0 °C. Immediately after immersion the RF power was switched on (1·8 W cm^{-2} continuous) and the tumour temperature settled at 43·0 °C within 4–5 min. This temperature was maintained within $\pm$ 0·1 °C for a period of 1 h. This system is clearly suitable for heating single tumours to a desired temperature, and is now being developed to allow simultaneous heating and individual thermostatic control of 16 separate tumours.

This work was entirely supported by the Cancer Research Campaign. We would like to thank Professor J. F. Fowler and Dr J. Denekamp at the Gray Laboratory and Dr J. W. Hand at the MRC Cyclotron Unit, Hammersmith Hospital, London, for helpful discussions.

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