Local Hyperthermia with Interstitial Techniques

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Abstract

The heating of deep visceral tumors with implanted electrodes and with self-regulating ferromagnetic thermoseeds was investigated. Clinical trials on six patients heated with implanted electrodes indicate that good local tumor control can be obtained by application of hyperthermia during a normal course of radiotherapy. The heating method was found practical, and neither toxicity nor severe patient discomfort was encountered. However, temperature inhomogeneity within the tumor volume remains a problem. Theoretical studies and an animal experiment indicate that temperature homogeneity can be largely improved by heating the tumor with thermoseeds made of an alloy of 70.4% nickel and 29.6% copper. The highly temperature-dependent rate of heat production in the vicinity of the Curie point, about 50°C for this material, provides automatic temperature regulation.

Introduction

In local hyperthermia, one seeks to elevate the temperature of the tumor-bearing region while leaving the temperature of other areas unchanged. To date, there is no noninvasive method available which can reliably achieve that goal in every clinical situation. Therefore, despite obvious disadvantages, invasive methods may be best for heating some tumors. In recent years, many invasive methods have been suggested. These include passing electrical currents between implanted metallic electrodes (3, 6–8), implanted microwave antennas (9), and thermal seeds (1, 2, 8). Technically, the implanted electrode method is probably the simplest one. The electrodes can be made of many kinds of readily available materials, e.g., surgical suture wire, while virtually any radiofrequency (RF) generator capable of producing 50 watts or more can be used as the power source. It can be shown with a mathematical model that this method is capable of heating tumors to a rather uniform temperature, provided that they have negligible blood flow and are surrounded by tissues with high blood flow (3). Since these conditions may be reasonably well satisfied in some lung tumors, we used this technique to treat a number of patients with pulmonary lesions. We will report on that in the first part of our paper.

In the thermoseed technique, an array of ferromagnetic needles is implanted into the tumor. The patient is placed into a magnetic induction field which produces heat within the needles. The heat is transferred to the tissues by thermal conduction. The absence of any electrical connecting wires between the implants and the power source makes this heating method very practical, especially when deep-seated tumors are treated. An additional advantage is that one can obtain thermal regulation by making the implants from a material having a ferromagnetic to nonferromagnetic transition (Curie point) at the desired tumor temperature. As the Curie point is approached, the implants begin to lose their ferromagnetism, and thereby their rate of heat production decreases (4). The automatic regulation offered by this mechanism should lead to better temperature homogeneity, especially in tumors with nonuniform blood perfusion, or in the presence of accidental irregularities in the implant arrangement. In the absence of any temperature regulation, as is the case with thermoseeds of stainless steel, areas having poor blood perfusion or containing too many thermoseeds would overheat, while the opposite would be true for regions having a high rate of blood flow or containing too few implants. Self-regulating thermoseeds, on the other hand, adjust their rate of heat production to the particular environment, and thereby compensate for unpredictable variations in the blood flow or unavoidable irregularities in the implant arrangement. In the second part of this paper, some of the physical aspects of this promising method will be discussed, and the results of an initial animal experiment will be described.

Interstitial Hyperthermia: Implanted Electrodes

Theoretical studies (3) indicated that a centrally located tumor, having negligible blood flow and being embedded in tissues with a high rate of blood perfusion, can be heated to a uniform temperature by a combination of implanted and external electrodes. This model requires that an internal electrode be located within the tumor mass, close to its surface. An external electrode surrounds the lesion at some distance from the tumor surface. If the tumor is located fairly symmetrically within the outer electrode, the surface of the internal electrode reaches a uniform temperature. Heat is then transferred to the center of the mass by conduction. We have approximated the requirements of this model by using an array of stainless steel wire or needles within the tumor, and a sheet of aluminum foil at the skin as the external electrode. This model suggests that internal implant geometry is not important as long as the needles or wire are placed closely enough to form a Faraday cage.

We have treated 6 patients with this technique. Five patients had non-oat cell lung cancer, and the sixth had a pelvic liposarcoma. All the lung cases were subjected to thoracotomy in an attempt at resection. When the surgeon determined that the mass was unresectable, he then fashioned an internal electrode by weaving stainless steel multifilament through the tumor (Fig. 1), exteriorized the lead wires (coated with polytetrafluoroethylene), and implanted thermocouples in tumor and normal lung. All patients then were treated with a course of radiotherapy (5000 rads/5 weeks) and hyperthermia.

The tumor was heated 10 times during the radiation course, each fraction lasting 1 hr and being given immediately after the
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Fig. 1. Internal wire electrode in lung cancer.

Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Av. maximum temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tumor</td>
</tr>
<tr>
<td>1</td>
<td>42.5°</td>
</tr>
<tr>
<td>2</td>
<td>45.9°</td>
</tr>
<tr>
<td>3</td>
<td>41.8°</td>
</tr>
<tr>
<td>4</td>
<td>40.9°</td>
</tr>
<tr>
<td>5</td>
<td>42.9°</td>
</tr>
</tbody>
</table>

The numbers in each column represent the average value (averaged over all 10 hyperthermia treatments) of the highest temperature recorded during each treatment in the respective tissue.

The abbreviation used is: RF, radio frequency.

The sixth patient had a centrally located 9-cm liposarcoma, recurrent after multiple previous interventions. The internal electrode was fashioned by inserting (transvaginally and transrectally) an array of 18-gauge stainless steel needles into the tumor mass. Each needle had a lead wire, and thermocouples were placed into several of the needles. The external electrode was a sheet of aluminum foil wrapped around the patient’s abdomen. The patient received 2000 rads over a 4-week period with hyperthermia given immediately after radiation, twice a week for 1 hr. Needle temperature ranged from 43 to 46° during each treatment. The patient experienced no major discomfort during treatment.

All patients had objective evidence of tumor regression. Four of the 5 lung patients have since died of distant disease, but no patient progressed in the volume treated with both radiation and hyperthermia. The fifth patient remains alive and well without evidence of carcinoma 1 year after treatment. The sixth patient’s mass shrank from 9 to 4 cm over a 6-month period, with resolution of her rectal bleeding and pain. She has recently shown some regrowth at the pelvic site and has developed distant metastases.

Thermoseed Technique

Induction Field Intensity and Frequency

When a tumor-bearing region containing implanted thermoseeds is exposed to a magnetic induction field, eddy currents are induced. The power dissipation by currents flowing within the thermoseeds causes the desired heating effect. However, eddy currents also flow within body tissues and thereby heat the daily dose of radiation. For each heat treatment we merely wrapped the patient’s chest in aluminum foil and connected the foil and the internal electrode lead wires to a RF3 generator. Temperatures were monitored with the previously implanted thermocouples. Table 1 shows the average maximum tumor temperature for each of the 5 patients. It was obtained by recording the highest temperature reading during each treatment, and by averaging these values over all 10 treatments. The individual maximum temperatures for each patient were rather consistent, varying typically by less than 0.3° from treatment to treatment. A few cases had more than one thermocouple in the tumor; these showed considerable inhomogeneity in intratumor temperature. Limiting toxicity during treatment was usually warmth or vague burning in the chest, especially in patients with pleural-based lesions. No heating of normal lung was seen.

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entire region exposed to the induction field. The rate at which heat is generated per unit volume of tissue, $P$, can be shown to be proportional to the square of the product of the magnetic field amplitude, $H_0$, times the magnetic field frequency, $f$, times the "radius," $R$, of the region exposed to the induction field, or $P \sim (H_0 \cdot f \cdot R)^2$ (1). This implies that in order to prevent undue heating of healthy tissues, the product $H_0 \cdot f$ must be maintained below a certain value, depending on the radius of the treated region and on the maximum tolerable tissue temperature. Thus, because of the relatively small radii of extremities, one can use higher frequencies and/or higher field intensities than in the treatment of diseases in the chest or abdomen. The wider range of acceptable frequencies and field amplitudes leaves more flexibility in the choice of the material for and the radius of the thermo-seeds. However, it is very desirable for a hyperthermia system to use a sufficiently low field amplitude and frequency so that the same apparatus can be used to treat tumors within the trunk as well as in the extremities. In such a system, the value $H_0 \cdot f = 4.85 \times 10^8$ A/m-sec should not be exceeded (1). Our system operates at $H_0 \cdot f = 3.85 \times 10^8$ A/m-sec, well below that level.

**Power Required to Heat Tumors**

In order for thermoseeds to heat a given tumor to the desired temperature, the implants must be capable of supplying a certain minimum amount of heat. The level of required heating power depends on the desired temperature elevation, on the blood flow within the lesion and the surrounding tissues, on the spacing between the implants and, to a lesser extent, on the tumor and implant geometry. Computations on a theoretical model and our clinical experience with tumors heated by implanted needle-shaped electrodes suggest that a heat power of about 50 milliwatts/cm implant length is in most cases enough to produce a temperature elevation of 10°C (2,7).

**Heating Power Produced by Thermoseeds**

The rate at which heat is produced by a cylindrical thermoseed depends on its radius, on its magnetic permeability, and on the intensity and frequency of the applied induction field (5). The rate of heat production generally goes up if any one of these parameters is increased. Furthermore, the heating power depends strongly on the orientation of the implant with respect to the magnetic induction field. In the perpendicular orientation, heat production is generally low, and only relatively thick thermoseeds having the proper magnetic permeability can satisfy the requirements. In the parallel orientation, power production is many times higher, and induction field frequencies of about 200 kHz or less are especially advantageous (1). At these low frequencies, the $H_0 \cdot f$ product can be maintained low, the implants can be made very thin (≤0.1-mm radius), and there are no stringent requirements on their magnetic properties. Thus, patient discomfort due to eddy current heating of healthy tissues should be insignificant, and tissue injury during the implantation procedure would be kept at a minimum. Also, the needles can be made from readily available materials, e.g., wire of stainless steel No. 430.

**Thermal Self-Regulation**

An ideal thermoseed would produce a large amount of heating power below the target temperature and no heat above it. The high-power production would assure that the target temperature could be reached in every conceivable situation, while the lack of heat production above it would prevent exceeding the desired temperature. In essence, an ideal thermoseed would always maintain a precisely defined temperature. In practice, one cannot expect the power versus temperature curve to exhibit this idealized step-function behavior. However, to obtain maximum temperature stabilization, the power-temperature curve should be as steep as possible in the vicinity of the Curie point.

If the temperature-dependent magnetic properties of the thermoseed material are known, the power produced by the implants can be calculated at any desired temperature (5). Chart 1 shows the heating power as a function of temperature, computed for thermoseeds consisting of an alloy composed of 70.4% nickel and 29.6% copper. Throughout the computations the $H_0 \cdot f$ product was assumed to be $4.85 \times 10^8$ A/m-sec. The relevant magnetic properties of the alloy were measured with a laboratory-built magnetometer. It can be seen that the slopes of the power curves increase as the induction field frequency and the seed radii are lowered. At the same time, however, the power production decreases. Therefore, a practical hyperthermia system must make a compromise between the conflicting requirements of a steep heat production curve and a satisfactory amount of heating power. We have chosen to operate our system at an induction-field frequency of 90 kHz, field intensity of $3.98 \times 10^8$ A/m (=50 oersted), and to use 0.45-mm radius thermoseeds. The computed power production curve for our system is very similar to that for 100 kHz, 0.5-mm seed radius, shown in Chart 1. We have verified our computations by measuring the heating power with a calorimetric method. The agreement between the computed and the measured heating power is quite good.

![Chart 1](cancerres.aacrjournals.org)
Biocompatibility

In some cases it may be preferable to leave the thermoseeds in place indefinitely, eliminating the need for a second surgical procedure to remove the implants. This would also make it relatively convenient to retreat the area in case of residual or recurrent disease. To prevent problems with toxicity, the implants should be either made of a biocompatible material or be covered with a biocompatible coat. If a coat is required, it should be strong and adhere well to the base material so that it would not peel off during the implantation procedure or at a later point in time. Furthermore, the coat should readily conduct the heat generated by the thermoseeds to the surface and should not interfere with the magnetic induction field. If the latter 2 requirements are not satisfied, thermal self-regulation is compromised.

Prolonged tissue contact with nickel-copper alloys may have toxic effects. We therefore intend to electroplate our implants with an alloy consisting of 55 atom % gold and 45 atom % silver. Pure gold or silver should not be used. Because of their high electrical conductivities, strong eddy currents would be induced in the coat, even if it were only 5 µm thick. These currents would produce considerable heat and would partially shield the magnetic induction field from the underlying nickel-copper alloy, resulting in poor thermal regulation. A thinner coat should not be used, since layers thinner than about 5 µm tend to be porous. The proposed gold-silver alloy has an electrical resistivity approximately 7 times higher than that of either of its 2 components. Preliminary computations indicate that a 5-µm-thick layer would have only a minor effect on the thermal self-regulation of our seeds. We are also investigating the possibility of coating our needles with Teflon and other organic materials.

Magnetic Induction System

High-frequency induction fields can be generated by a circuit consisting of an induction coil with a capacitor connected in parallel, driven by a RF generator at the resonant frequency. To be versatile in clinical hyperthermia applications, the coil should be large enough to encompass any segment of the human body. For that reason we use in our apparatus an induction coil having an elliptical cross-section with a major axis of 48 cm and a minor axis of 42 cm (Fig. 2). To minimize the power required to drive the system the coil is 45 cm long. (It can be shown mathematically that a coil having a length equal to its diameter requires the least amount of RF power to produce a given field intensity at its center.) Our coil has 9 windings, made from a 36-mm-wide strip of copper sheet. A one-fifth horsepower blower, mounted above the coil, removes the 1.5-kilowatt heat dissipated during normal operation at 90 kHz, 3.98 × 10^2 A/m field amplitude at the coil center. The resonant capacitor is located below the coil. To prevent arcing, it is submerged under transformer oil.

A hyperthermia treatment with our present system requires that the patient be placed into the induction coil, an arrangement which produces a magnetic field parallel to the patient “axis.” Since the thermoseeds function properly only when aligned with the induction field, the surgeon must implant them parallel to the patient axis. In certain cases this may be much more difficult to do than to place them perpendicular to the patient. We are therefore designing an induction system which would allow the magnetic field to be applied at right angles to the patient.

Preliminary studies of an apparatus using 2 coaxially arranged coils suggest that such a machine would be substantially larger than our present one and would consume about 10 kilowatts RF power, even if all design parameters (coil radii, coil lengths, and current density within the coils) were optimized for minimum power consumption. The power consumption could be reduced by operating at a higher induction field frequency. However, this would compromise the thermal self-regulation and may require needles with radii larger than 0.45 mm.

Application of Thermoseeds to in Vivo Treatment

We have investigated the application of self-regulating thermoseeds in a dog model. We implanted an array of 13 needles plus several thermocouples into a ligated dog kidney, which simulated a small, poorly perfused visceral mass. The needles were arranged parallel to the long axis of the animal. The abdomen was closed and the dog was then placed into our magnetic induction coil in such a way that the needles were parallel to the direction of the magnetic field. RF power was applied, and the temperature was monitored to equilibrium. The temperature in the kidney rapidly escalated and stabilized at 50°, approximately the Curie point of the alloy. A temperature profile within the kidney showed that equilibrium temperatures were uniform to ±10%. Additional thermocouples in the liver and s.c. tissues showed no evidence of direct inductive heating. All temperature elevation was confined to the immediate vicinity of the thermoseeds. These findings are well in line with theory. Considering the ligated kidney as a tumor with low blood flow, one would expect the maximum temperature to lie between 49.5 and 50.5°, depending on the thermal properties of the surround-
ing tissues. The temperature throughout the tumor should fluctuate by about 1° and fall off very rapidly beyond the tumor margin.

Discussion

It has been demonstrated that it is clinically feasible to heat deep visceral tumors with a combination of implanted and external electrodes. The implants caused our patients virtually no discomfort, nor did we observe any other severe complications. In contrast to external heating techniques, the required heating power was very low, which may be the reason why the hyperthermia treatments were so well tolerated. Increases in systemic temperature, anxiety, and nausea, occasionally observed during treatment with external methods requiring 300 watts or more of RF power, were practically nonexistent. The observed inhomogeneities in the tumor temperature can be attributed to the presence of appreciable blood flow and to large gaps in the weaving of the internal electrode. It is encouraging that despite these temperature inhomogeneities, local tumor control was remarkably good.

The results of our initial animal experiment with self-regulating thermoseeds are very promising. The good agreement with the computed temperature distributions suggests that one can make valid estimates of the clinical performance of the thermoseed technique. According to these the thermoseed technique should be a very useful and practical means for inducing hyperthermia. Surgical implantation of the thermoseeds should be relatively simple, since there would be no requirement to connect the individual needles to an outside power source. During treatment the patients should be relatively comfortable and would not be overly limited in their ability to move. This should allow one nurse or technician to treat several patients at the same time, making this technique less labor intensive than many other methods. Furthermore, one should be able to closely approximate any desired temperature distribution throughout the treated volume. For example, by inserting implants with a high Curie point in the center of the tumor and “cooler” needles in the periphery, one could assure destruction of the tumor core without undue damage to vital structures infiltrated by the cancer at its margin. The necessary variations in the Curie point could be achieved by adjusting the copper content of the alloy.

Acknowledgments

The authors are grateful to Benjamin E. Blackburn for his expert advice during the preparation of the manuscript, and to Nancy Powell for her secretarial assistance.

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Cancer Res 1984;44:4752s-4756s.

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