Regional Hyperthermia: A Clinical Appraisal of Noninvasive Deep-Heating Methods

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Abstract

The concentric single-turn self-resonant coil operated at 13.56 MHz (CC) and the annular array applicator (AA) operated at 55 to 100 MHz are the only regional heating devices the clinical use of which has been subjected to sufficient thermometric characterization to be evaluable. The clinical heating characteristics and toxicity of both devices are reviewed. When spatial temperature measurements have been made during clinical treatments with the CC, the observed temperatures have been consistent with theoretical predictions and phantom studies; temperatures fall with increasing radial depth, and potentially injurious heating in superficial normal tissues and ineffective heating in deep-seated tumor loci have been commonly observed. The CC is ineffective in heating central pelvic tumors due to inadequate penetration and power-limiting sacroccocygeal pain. The AA has been demonstrated to heat many deep pelvic tumors to maximum temperatures greater than 42–43°C without significant side effects, but further study is needed to determine the feasibility of achieving higher minimum tumor temperatures and longer treatment durations. In the upper abdomen, the AA appears to have a slight superiority in rapid tumor heating at depth, but both devices have major limitations with insufficient penetration (CC) or treatment limiting systemic heating (AA). There has been no adequately thermometrically documented experience with heating in the deep thorax with either device.

Introduction

Although the clinical efficacy of adjunctive hyperthermia in the treatment of cancer has not been unequivocally established, the weight of the evidence is heavily in favor of a significant improvement in complete tumor regression and response duration when hyperthermia has been combined with radiation therapy in the treatment of superficial tumors. Such evidence is exciting and tantalizing. Unfortunately, tumors which are heatable with readily available current techniques only occasionally pose a significant threat to the patient that cannot be adequately dealt with by surgery or conventional radiation therapy. To bridge the gap between clinically effective and clinically useful treatment, we must begin by learning how to heat deeper tumor locations where improved local control would be associated with better palliative or curative outcomes in substantial numbers of patients. At present, deep heating can be attempted with implanted antennae or electrode arrays, focused ultrasound, or noninvasive electromagnetic techniques. In the latter case, the long wavelengths, large applicators, and broad surface area coverage needed to achieve significant penetration result in unfocused regional heating. Oleson (5, 6) has reviewed the physical basis and laboratory documentation of the deep-heating characteristics of regional heating techniques. However, to proceed scientifically in our evaluation of hyperthermia, we must also document their clinical heating characteristics. During a time when electromagnetic noninteractive thermometry was extremely difficult or unobtainable, clinical applications of a number of approaches to deep heating have resulted in reports based on insufficient thermometry. These reports have created confusion as to the deep-heating capacity of these techniques. Several nonperturbing thermometry systems are now available, and using a technique called "thermal mapping" (2), whereby the thermometric probes are moved within small catheters traversing the tumor-bearing region to determine the temperature at various points under conditions of near thermal equilibrium, it is possible to gather a great deal of information concerning the clinically achievable tumor and normal tissue temperatures. Equally important as spatial temperature distribution is the rate of temperature rise and time-at-temperature. The mere statement of the temperature achieved is of little significance without the associated time factors. The objective of the present report is to review the available data pertaining to the clinical use of the regional heating techniques with an emphasis on patient tolerance and documentation of the capacity to produce satisfactory heating of the tumor and surrounding tissue. The discussion will center on 2 devices, a CC (Magnetrode; Henry Medical Electronics, Los Angeles, CA) driven at 13.56 MHz and an AA (BSD Medical Corp., Salt Lake City, UT) applicator driven at 55 to 100 MHz. These are the only regional heating devices which have been used clinically and subjected to sufficient scrutiny to be considered moderately evaluable. Other devices, as discussed by Oleson in another paper in this workshop (6), appear to have varying degrees of promise, but either have not been used clinically or have not been used with thermometry sufficient to permit evaluation.

Concentric Coil

Storm et al. (9–12) have published a number of optimistic reports regarding the heating capabilities of the CC, at one point claiming that it could heat uniformly to any depth (11) and that convective distribution of superficially deposited power and gradual heating led to uniform tumor heating. High tumor temperatures in humans were often reported in these studies. However, because the temperatures were not specifically related to anatomic location, depth, or the time necessary to achieve them, the authors' opinion that the CC is capable of effective heating at any depth is not supportable with their published results.

1 Presented at the Workshop Conference on Hyperthermia in Cancer Treatment, March 19 to 21, 1984, Tucson, AZ. This review was supported by USPHS Grant CA 29578 and Contract CM 17523.


OCTOBER 1984

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A more detailed report by Baker et al. (1) documented the maximum temperatures achieved in 99 patients treated with the CC. The temperature range was 37°-50°; 73% were above 41°, 54% above 42°, and 27% above 43°. The treatment duration was 30 min, but the times required to achieve the stated temperatures were not given. The temperatures were generally recorded at single points within the tumors, and no information pertaining to specific anatomic locations or depths was reported. Two point measurements within the tumor were said to differ by up to 2° when they were obtained. Intracavitary temperatures were also measured in the heated field, and the authors stated that they were "never significantly elevated and usually did not exceed the core temperature. It was believed that good mucosal blood flow in these structures provided a safety mechanism." The authors further stated that "the findings of Storm et al. that the Magnetrode can effectively heat tumors at any depth were confirmed in this study." For the reasons stated in the preceding paragraph, this claim is not supportable with their published data.

Twomey and Frey (13) reported a series of 19 patients in which 104 paired temperature measurements were obtained from tumors and adjacent normal tissue. In only one-third of the patients was it possible to achieve an intratumor temperature of 42° or greater. They observed intratumor temperature variations of 1 to 3°, a trend toward decreasing temperatures at depth, and no significant mean differential temperature between normal tissue and tumor.

In contrast to the previous report, Khandekar et al. (3) reported temperature measurements from 14 patients who were treated with the CC for locally advanced pancreatic carcinoma. The reported patients had surgically implanted intratumoral temperature monitoring catheters placed at depths of 5 cm or greater from the skin. The authors were able to achieve an average maximum temperature of 43.9°; however, duration at temperature and temperature variations with depth were not stated.

Oleson et al. (7) reported on a series of 31 patients treated with the CC for bulky cancers refractory to conventional treatment. This study is the first to report spatial thermometry in the use of the CC. In 3 patients, they were able to raise all of the measured intratumor points to greater than 42.5°. In 6 patients, some of the intratumor temperatures were greater than 42.5°, but in 22 they were unable to achieve this temperature at any measured point within the tumors. Two of the 3 patients in which heating of the entire tumor was achieved were in limbs, a small diameter site where more uniform heating would have been anticipated. In 8 cases, measurements of power density (which are directly proportional to the initial slope of the temperature rise at a given point within the tumor) were observed to fall with increasing depth as did the intratumor temperature achieved. Based on measurements of the power density required to maintain the periphery of the treated tumor at 42.5° and the power density distributions measured from a model of human pelvic anatomy, the authors concluded that the maximum depth that the superficial edge of a tumor similar to those they measured could be located and still be potentially heatable to 42 to 43° was approximately 7 cm (range, 0 to 9.5 cm). The authors also emphasized the stressful nature of the treatment with most patients complaining of local pain and fatigue. Of particular note is the apparent consistency of their heating results with those of Baker et al. (1). In the former, 29% of their cases achieved intratumor temperatures of 42.5°, and in the latter the comparable figure was 36%. These percentages are quite similar and suggest relative comparability in the way the treatments were performed. However, in two-thirds of the patients so heated by Oleson et al. (7), only part of the tumor exceeded 42.5°. This suggests that, in the cases reported by Baker et al. (1), there were regions of temperatures cooler than those reported in most of the tumors.

The AA

The AA is a newer device than the CC, and although reports of its clinical application are more limited, it has been studied in greater detail in terms of its heating capabilities and side effects. Sapozink et al. (8) reported its use in 46 patients with advanced pelvic and abdominal cancers. Due to the fact that the reported experience occurred early under a variety of adverse clinical circumstances, there were only 22 patients included in the thermometry analysis. This aspect of the study addressed patients who had completed a mean of 5 treatments each so that the heating characteristics of a series of treatments could be reported. The authors listed a variety of reasons for exclusion of cases from the thermometry analysis, but in only 3 cases were treatments discontinued due to unfavorable tumor versus normal tissue heating. The 3 major reasons for exclusions were that the patients: (a) were too debilitated to tolerate treatment; (b) were treated only incidentally on the AA in comparison with other forms of equipment; or (c) had insufficient thermometry performed early in the study.

The thermometry was performed using high-resistance lead thermistor probes and a semiautomated thermal mapping technique (2). Thermometry catheters were inserted percutaneously or intracavitarily and usually under computed tomographic guidance so as to maximize the relevance of the tumor and normal tissue temperatures obtained from each catheter. Although the ideal treatment intent was to maintain minimum tumor temperatures of 42-43° for 30 min after induction, a high priority was placed on avoiding potential injury, so heavy sedation and analgesia were avoided, and power was reduced or the treatment terminated in the case of significant discomfort or major physiological stress.

One-half of the patients were categorized as having abdominal disease (generally supraumbilical) and one-half, pelvic. The time required for some tumor point to reach 41° averaged 19 min in the pelvis and 26 min in the abdomen. All tumors achieved temperatures at least this high. Nine pelvic and 5 abdominal tumors achieved temperatures of 43° or greater, and in 2 other abdominal cases temperatures were either attained or readily attainable. The average induction times to reach 43° were 27 min in the pelvis and 32 min in the abdomen.

In all but 3 cases, it was possible to raise all of the monitored tumor points to over 41° at some point during the treatments, but in only one case was it possible to achieve the same goal with 43°. Upon further examination of the results of the best single treatments, it was possible to achieve 43° in over one-half of the intratumor points sampled. Overall, during the entire course of treatments, it was possible to equal or exceed 41° at
75% of the pelvic tumor points and 63% of the abdominal. For 43°, the proportions were 29 and 22%, respectively. The mean time that it was possible to hold tumor temperatures at 43° or above was only 14 min in the pelvis and 12 min in the abdomen.

The authors defined a "quality factor" (Q) as the product of the mean sampling fraction of temperatures exceeding a given index temperature and the length of time it was possible to maintain such temperatures divided by the target time of 30 min. The optimal Q would be equal to one if all tumor temperatures equalled or exceeded the index temperature for 30 min. The Q values for 41° were 0.7 in the pelvis and 0.55 in the abdomen; for 43°, they were 0.13 and 0.12, respectively. Obviously, not all intratumor points could be monitored, and there was no way to determine whether the indicated sampling fractions were an accurate reflection of the actual temperature distributions throughout the tumors.

Although no significant persistent side effects were noted, patients experienced an assortment of discomforts which were often power limiting. In the pelvis, complaints usually consisted of various pains originating within or about the applicator aperture. In the abdomen, the major side effect was systemic stress (e.g., anxiety, malaise, tachycardia) due to high core temperatures with a mean maximum p.o. temperature of 39.4° and a mean normal tissue maximum in the heated volume of 41°. In the pelvis, the mean maximum systemic p.o. temperature was only 38.2° with a mean normal tissue maximum in the heated volume of 42.6°, indicating a slower systemic redistribution of power than in the upper abdomen.

Comparison of the AA and the CC

In a recently reported study from the University of Utah Medical Center and the LDS Hospital in Salt Lake City, 22 patients with advanced abdominal or pelvic cancer were heated in both the AA and CC. The objectives of the study were to: (a) record spatial temperature distributions at identical sites in the same patient treated with each device on successive occasions; and (b) compare acute toxicity and power-limiting factors associated with each device in each patient. The thermometry analysis was again divided into anatomical regions of pelvis and abdomen. Thirteen patients with pelvic sites, 8 with abdominal sites, and one with both regions requiring treatment were studied. Thermometry catheters were placed percutaneously (generally under computed tomographic guidance) or in accessible body cavities. A few patients had more than one percutaneous catheter placement in different locations. Positions of normal tissue and tumor loci were specified according to their depths along each catheter.

The high-resistance lead nonperturbing thermistor probes were used with a manual thermal mapping system with the AA. Gallium arsenide fiberoptic probes were used with a semi-automated thermal mapping system with the CC. Measurements were made from the same catheter left in place between comparative treatments. Thermometry data were recorded during successive treatments separated by 1 to 5 days. The sequence of the device used and the exact time during the treatment course were variable and not controlled, since significant changes in heating patterns during postcomparative heating sessions were not observed. In addition to spatial temperature measurements, a thermal dose distribution analysis was undertaken on all cases where data were sufficient and where the adequacy of heating with either device was judged sufficient to warrant careful analysis (i.e., where some measured point within the tumor was shown to have achieved the equivalent of 30 min heating at 42.5°). To calculate the thermal dose distributions, the thermal mapping data were converted to a series of temperature-time curves for each point at 1-cm intervals along the catheters. Each curve was then subjected to analysis according to the following:

\[
\text{Thermal dose} = \int_0^{t_{\text{end}}} F(T) \, dt
\]

where \( F(T) \) is a thermal equivalence factor, \( T \) is temperature, and \( t \) is time (min), and \( F(T) = 0 \) (where \( T < 40° \)), \( e^{-(42.5 - T)/0.5} \) (where \( 40 < T < 42.5 \)), 1 (where \( T = 42.5 \)), \( e^{-(42.5 - T)/0.5} \) (where \( 42.5 < T < 45.5 \)), and 8 (where \( T > 45.5 \)). Although there may be objections to this thermal dose formulation on thermobiological grounds, such objections are largely irrelevant in the context of using this approach to rapidly convey the temperature-distance and temperature-time parameters of a given treatment, where it is extremely useful.

Patients were not heavily premedicated or sedated for treatments with either device, and those who experienced potentially more discomfort were asked to be tolerant for as long as possible before requesting a reduction in power. In order to avoid injury, patients’ complaints were frequently power limiting, and patients were rarely given increased analgesia or sedation to permit escalation of power output. Since specific complaints were generally different with the 2 devices, it was difficult to assure comparable determinants of the limitation on applied power. In most cases, treatments on the CC appeared to be associated with a slightly higher level of discomfort than the AA. Treatments on the CC were administered at maximum tolerable power for 30 min with occasional power-off periods for several min for subjective relief as required. Treatments were occasionally shorter when it was clear that plateau temperatures had been reached and effective heating could not be achieved. If heating appeared to be effective and well tolerated and it was apparent that additional heating time would result in higher temperatures, the treatment was continued for longer than 30 min until plateau temperatures were achieved.

In the case of the AA, although the intent of treatment was >42° tumor temperatures for 30 min postinduction, this goal was generally not achievable within the constraints of patient tolerance. Although it was difficult to standardize the treatment endpoints in an exactly comparable manner between the 2 devices, the average treatment durations overall were similar and the highest temperatures tolerable and considered safe were achieved with both devices in every treatment.

The average maximum temperatures achieved in radial catheter placements in the abdomen and pelvis are shown in Chart 1. Maximum temperatures with the CC generally occurred 1 to 3 cm from the skin surface (usually in normal tissue) and decreased with increasing depth. In the case of the AA, greater temperature elevation was seen with increasing depth, primarily due to the larger proportion of poorly perfused intratumor points with increasing depth contributing to the data.

Chart 2 shows the maximum temperatures achieved in cath-
Chart 1. Means of the best heating patterns achieved in abdominal and pelvic tumors measured in percutaneously placed catheters positioned radially. Fourteen radial probes were used in 13 patients.

Chart 2. Means of the best heating patterns achieved in abdominal and pelvic tumors measured in percutaneously placed catheters positioned nonradially along a chord intersecting the arc of the patient’s cross-sectional circumference. Six probes were used in 5 patients.

Chart 3. Means of the best heating pattern achieved in pelvic tumors measured in rectal or posterior perineal locations. Six probes were used in 6 patients.

Chart 4. Means of the best heating pattern achieved in pelvic tumors measured in the bladder and urethra, vagina, or anterior perineal locations. Seven probes were used in 4 patients.

Chart 5. Example of “thermal dose” distributions from a single patient treated on both the annular array and concentric coil; ———, level of the “target thermal dose” of 30 equivalent minutes at 42.5°C; ———, depth and thickness of the tumor traversed by the thermometry catheter.

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Table 1

<table>
<thead>
<tr>
<th></th>
<th>Mean thermal dose analysis</th>
<th>Therapeutic ratio (TD_{tumor}/TD_{norm})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tumor TD_{max}</td>
<td>TD_{tumor}</td>
</tr>
<tr>
<td>Abdominal</td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>10.4</td>
<td>30</td>
</tr>
<tr>
<td>CC</td>
<td>1.8</td>
<td>23</td>
</tr>
<tr>
<td>Pelvic</td>
<td>(7)</td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>24</td>
<td>95</td>
</tr>
<tr>
<td>CC</td>
<td>0.5</td>
<td>22</td>
</tr>
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the CC, particularly with regard to the minimum tumor thermal dose (since in most cases some areas of the tumors were virtually unheated by the CC) and the therapeutic ratio (particularly in the cases where temperatures were measured by radial percutaneous catheters where prominent superficial tissue heating was present with the CC).

In terms of side effects, the authors noted similar symptoms and power-limiting factors to those described previously for the AA. The most striking observation of the side effects with the CC was that nearly every patient heated in the pelvic region had power-limiting sacrococcygeal pain possibly caused by constriction of current paths in the sacral region as modeled by Oleson (4). In general, the treatments on the CC tended to be a more painful experience, whereas the treatments on the AA were more anxiety-provoking and physiologically stressful due to the larger effectively heated volume, higher power levels, and more constraining apparatus.

Conclusion

The CC heats more effectively near the surface of the body, probably particularly in the muscle annulus of the abdomen and in tumors which involve the muscle at this site. Temperatures and power densities fall with increasing depth, and effective heating at deep-seated tumor loci is rarely achievable. Although the effective heating depth will depend on tumor perfusion, radial depths greater than 7 cm would not ordinarily be expected to be heated to potentially therapeutic temperatures.

Heating with the CC frequently produces higher temperatures in superficial normal tissue than in deeper tumor, although surface and s.c. fat heating is not a problem.

Heating in the pelvic region is particularly limited with the CC due to ineffective central power deposition and severe sacrococcygeal pain. Some tumors lying just anterior to, or adherent to, the sacrum may be heatable, but tumors in the vicinity of the bladder and vagina are not.

There is no published evidence in humans that local or regional blood flow substantially influences the ability of the CC to heat tumors at greater-than-anticipated depths through convective redistribution of heat from more superficial tissues. Deep-seated tumor points are frequently so ineffectually heated that more protracted heating times would be expected to cause little additional temperature rise at these points.

The observation of the lack of effective intracavitary heating in the bladder, rectum, stomach, etc., by the CC is most likely due to low power densities at the associated depths rather than the protective effect of high mucosal blood flow as proposed by Baker et al. (1).

Apparent discrepancies in the literature regarding the ability of the CC to heat uniformly at depth appear to be readily explainable by the extent of the thermometry performed in the studies in question. As with most heating techniques, the less one knows about the spatial temperature distribution, the more impressed one will be by the apparent efficacy of the technique.

Further investigations of the efficacy of heating with the CC in the region of the pancreas using thermal mapping techniques will be necessary to determine whether the temperatures reported by Khandekar et al. (3) are representative of the deeper paraspinal tumor regions.

The potential for thermal dose escalation with the CC appears limited without risking burns in differentially heated superficial normal tissues.

The AA is a far more complicated instrument than the CC, and we are still learning to properly control the many parameters which may affect the optimization of its performance.

In the pelvic region, the AA seems to have particular promise. Effective central pelvic temperatures can often be reached and, since measured normal tissue temperatures have seldom been power limiting and injuries have not occurred, dose escalation with more effective sedation and analgesia is a realistic option to increase tumor temperatures and treatment durations. Since systemic heating has not been a problem, the addition of systemic hyperthermia could also be advantageous in increasing pelvic temperatures. However, possible thermal injury as well as enhanced normal tissue reactions to radiation and/or chemotherapy may occur during this process of dose escalation.

In the upper abdomen, the AA appears to have a slight edge over the CC, primarily in terms of thermal dose analysis and therapeutic ratio, but additional studies are needed. At present, both instruments have substantial deficiencies. The CC lacks sufficient penetration, and the broad regional heating characteristics of the AA result in power-limiting systemic heating and associated symptoms in this highly perfused region of the body. It appears that neither instrument will have much success in heating deep-seated tumors in the upper abdomen that have relatively normal rates of perfusion. Effective systemic cooling has already been used in the studies reported with the AA, and it is uncertain how much additional cooling will add. Confinement of the heated volume through reduced surface coupling and steering of the power density patterns through circumferentially nonuniform power application or phase alteration would seem to be realistic options for further study.

Neither the CC nor the AA have been well studied in deep thoracic regions, and the water bolus configuration required for electromagnetic coupling to the patient in the AA may make treatment in this region technically difficult.

Regional hyperthermia as presently practiced is an uncomfortable and highly taxing procedure for most patients. It is often painful (particularly with the CC) and physiologically stressful (particularly with the AA) and requires great motivation on the part of the patients. Positional constraints on the patient by the AA are also a significant disadvantage. It is not a procedure that one can apply to most elderly or debilitated patients with advanced cancer and be able to achieve the thermal dose distributions anticipated to be necessary to achieve a potentially curative outcome in combination with drugs or radiation therapy. When properly practiced in the research setting with the necessary continuous patient monitoring and temperature documentation, it is a lengthy, intensive process for the patient, the physician, and the technical assistant. Although therapeutic benefit can be reasonably attributed to regional hyperthermia in selected cases, the ultimate demonstration of its potential therapeutic efficacy will depend on appropriate clinical trials based on the scientific and accurate use of effective heating devices. To rigorously test the therapeutic efficacy of a device with undocument heating characteristics would be to risk years of wasted effort.

References

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_Cancer Res_ 1984;44:4765s-4770s.

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